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EDITORIAL COMMENT

Endothelial Function and Shear Stress

Which Came First, the Chicken or the Egg?*

Juan Luis Gutiérrez-Chico, MD, PhD[a,b]

Research in atherosclerosis has classically put the focus either on systemic or locoregional factors. The former approach considers atherosclerosis as a systemic process involving the whole arterial vasculature and concentrates prevention efforts on the vulnerable patient, rather than on other anatomic concepts such as the debated vulnerable plaque (1). Perhaps it is fair to admit that this systemic approach has succeeded in translating into clearer practical directions for prevention than the locoregional approach, which, irrespective of its conceptually appealing rationale, has as of yet failed to generate clinically compelling evidence. Nonetheless, the locoregional factors cannot be neglected: intracoronary biomechanics, namely shear stress (SS), is a potent stimulus for the endothelium that determines the plaque distribution within the vessel (2,3), particularly in some anatomic scenarios with uneven SS distribution (e.g., curved vessels, bifurcations) (3–8). Moreover, the regional SS is inversely related to the thickness of the neointima after stenting in bare-metal stents (9), drug-eluting stents (10–12), and bioresorbable scaffolds (13,14). Unfortunately, the concept of SS is also often misused as a conjectural explanation for any kind of puzzling findings: whenever the interventional cardiologists do not understand why something happens, they blame SS, as an intangible esoteric force, as difficult to prove as it is to discuss.

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In this issue of the *Journal*, Siasos et al. (15) present an elegant study that expands the current understanding about the role of SS in atherogenesis by proving its association with both epicardial and microvascular endothelial dysfunction. We must concede to the authors that they have proved the association beyond any doubt. Nonetheless, although the link of SS to epicardial dysfunction (defined as vasodilation/vasoconstriction) raises no concern, the association with microvascular dysfunction (defined as an increase in coronary flow) must be carefully scrutinized because SS depends itself on coronary flow. The authors might have just performed a futile exercise in tautology, correlating 2 variables (SS and microvascular function) which are indeed functions that are both dependent on a third variable (flow). Nevertheless, this scenario is not the case. First, SS is calculated as a function of basal flow, while the microvascular dysfunction is calculated as the proportional increase in flow after infusion of acetylcholine (i.e., 2 different flow conditions). Because there are no differences in basal flow between patients with or without microvascular dysfunction, confusion can be ruled out, and the association is valid. The interpretation of this finding becomes difficult, but the association exists. Furthermore, the reported association (the lower the SS, the lower the increase in flow) goes against the potential self-correlation that could be expected from a strictly mathematical (not biological) point of view (the lower the SS, the higher the chance to increase the flow).

Although we cannot dispute that Siasos et al. (15) proved the association, the interpretation of these findings is, however, utmost difficult. The pathophysiological interpretation proposed by the authors in Online Figure 4 (15), considering SS as an intermediate step between microvascular and epicardial endothelial dysfunction, is plausible and appealing, but the study is far from proving any causative relation. It could indeed be the other way around: vessels with lower SS could trigger some kind of signaling in the endothelium that accelerates both

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From the [a]DRK-Klinikum Westend, Berlin, Germany; and the [b]Punta de Europa University Hospital, Algeciras (Cádiz), Spain. Dr. Gutiérrez-Chico has reported that he has no relationships relevant to the contents of this paper to disclose.

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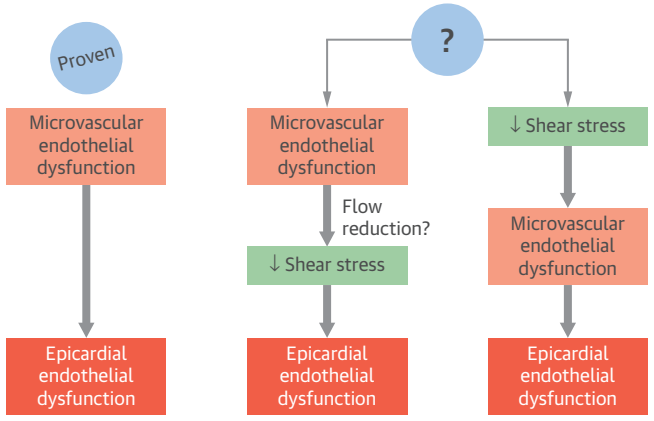
FIGURE 1 Pathophysiological Models of Atherogenesis Explaining the Study Findings



Data prove that microvascular endothelial dysfunction precedes epicardial endothelial dysfunction **(left)**. It is unclear what role shear stress can play in this process. One possibility is that the microvascular dysfunction reduces the shear stress, and this fact accelerates the development of epicardial endothelial dysfunction **(middle)**. In this case, the question is whether microvascular dysfunction may modify shear stress without reducing the overall flow. Other pathogenic models are also plausible, such as a primarily reduced shear stress, triggering signaling in the endothelium that accelerates the aforementioned process **(right)**.

microvascular and epicardial dysfunction (**Figure 1**). The question remains open and perhaps it will never be answered, just like the reciprocating question about which came first, the chicken or the egg.

Even more difficult to interpret in the authors' model (15) is how microvascular dysfunction can modify SS without having any influence on basal flow: the groups of normal versus abnormal microvascular function had no differences in basal coronary flow. This concept is methodologically convenient to prove the association between microvascular function and SS, but it ruins the pathogenic model in which microvascular dysfunction "modifies" SS. How? Without modifying the flow? Or do the authors imply that some anatomic configurations, with lower SS, are more prone to an accelerated atherosclerotic process? The interpretation is elusive. SS has been instrumental in understanding atherogenesis at a regional level, to explain why atherosclerosis is preferentially found in some regions of the vessel (e.g., the shoulders of a bifurcation or the outer curvature), but it is unclear how this regional force could play a role in global parameters affecting the whole coronary vessel, such as endothelial function, which is evaluated globally in the whole coronary vessel. Both epicardial and microvascular endothelial functions are evaluated per vessel, whereas SS is mapped throughout the vessel wall. Let us add then that there is no clear SS threshold that can be considered abnormal or atherogenic and that SS calculation is extremely sensitive to subtle methodological details, such as the computation of the flow through side branches (16). After that, the take-home message will probably be stuffed with question marks.

Skipping too deep philosophical conundrums, this study (15) contains a pearl, hidden among all the SS analyses: although patients with microvascular dysfunction might have epicardial dysfunction, no single patient with epicardial endothelial dysfunction had normal microvascular function. This simple but undisputable finding provides very interesting information about the pathogenesis of atherosclerosis, suggesting a functional beginning in the endothelium of small vessels, then progressing to the endothelium of epicardial vessels, and finally ending up in the tissue alterations previously described (17). This process is clear, irrespective of any biomechanical disquisition. We will probably need more evidence and more time to understand the hypothetical "butterfly effect" of a regional force on the vessel as a whole.

ADDRESS FOR CORRESPONDENCE: Dr. Juan Luis Gutiérrez-Chico, Cardiology Department, Punta de Europa University Hospital, Crtra. Getares s/n, 11207 Algeciras (Cádiz), Spain. E-mail: juanluis.gutierrezchico@ictra.es.

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