Protective or Destructive: High Wall Shear Stress and Atherosclerosis

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Intraplaque hemorrhage (IPH) is an emerging biomarker associated with high risk (vulnerable) atherosclerotic plaques. Prospective studies have identified IPH as a predictor for subsequent ischemic cerebrovascular events in both asymptomatic and symptomatic individuals [1, 2] and linked IPH to rapid growth of the lipid-rich necrotic core and accelerated progression of plaque [2, 3]. While our understanding of atherosclerotic plaque development is evolving, recent data have demonstrated that plaques which result in acute coronary events have larger plaque and necrotic core volume with greater expansive remodeling compared with asymptomatic plaques [4]. It is now believed that there is an accelerated plaque growth before acute coronary events. It is postulated that intraplaque neovascularization with leaking wall and subclinical cycles of rupture and healing are mechanisms of development of IPH and the accelerated plaque progression (Figure 1). In fact, along with luminal thrombus and plaque fissure, IPH is one of the main factors contributing to the sudden increase in plaque size ultimately resulting in the onset of acute coronary events [5].

Under physiological conditions, atherosclerotic plaque is subject to mechanical loading due to pulsatile blood pressure and flow. Studies have shown the pathological impact of mechanical stimuli on the bio-function of vascular endothelial cells (ECs) [6] and smooth muscle cells [7] that may further contribute to the initialization and development of atherosclerosis. In this issue of Atherosclerosis, Tuenter et al. examined the relationship between high wall shear stress (WSS) and plaque composition in 93 carotid arteries of 74 asymptomatic participants [8] from the Rotterdam Study, a general population-based study, and a very rare database of such kind. In this relatively large cross-sectional study, the fluid domain of each plaque was reconstructed based on 2D magnetic resonance images to perform computational fluid dynamic analysis. By relating the maximum value of WSS in each carotid plaque to the plaque composition, the authors used a simple analysis to present the complicated relationship between WSS and plaque composition. They found an association between higher maximum WSS in each plaque and the presence of IPH and calcifications, but not necrotic core,

independent of plaque thickness. Despite the inherent limitations of this cross-sectional study, these conclusions generally support the findings of two previously published human studies [9, 10], but are contradictory to another human study [11].

Different flow patterns directly determine EC morphology, metabolism, and inflammatory phenotype through signal transduction and gene and protein expression [12]. ECs are capable of perceiving WSS as a mechanical signal, transmitting this into the cell interior, triggering serial cellular signaling responsible for gene expression and then regulating the function of vascular smooth muscle cells [13]. Several animal and human studies in coronary and carotid arteries suggest a role for hemodynamic factors such as WSS in the evolution of atherosclerotic plaque. For years, WSS was categorized to low and high (non-low). Based on this, while there has been a consensus that low and/or oscillatory WSS results in atherosclerosis formation and progression [12], the so called "high WSS" was thought to be atheroprotective. In recent year, however, investigators categorized non-low WSS (previously called "high WSS") to physiologic WSS and high WSS; and investigated the role of higher than physiologic values of WSS in the development of atherosclerosis. Experimental studies have demonstrated that expansive remodeling stimulated by high WSS is part of a process resulting in thinning of the fibroatheroma cap and presumably preparing the environment for plaque rupture [14]. Data from a human carotid autopsy study demonstrated that high WSS segments co-localize with increased macrophages levels and plaque rupture [15]. In line with the experimental and autopsy studies, a longitudinal human coronary study showed overall plaque regression with an increase in plaque necrotic core and calcium and expansive remodeling in areas exposed to baseline high WSS [9]. Another small longitudinal study of human coronaries also observed an increase in plaque strain in those regions exposed to baseline high WSS [16]. In addition, in a small cross-sectional study of human coronary arteries, Wentzel et al. showed that plaques with large necrotic core and a necrotic core in contact with the lumen were more frequently exposed to high WSS [10].

The interplay between atherosclerotic plaque, artery, and WSS seems to be very

dynamic. However, because of the lack of natural history studies of atherosclerosis in humans, there are still many unanswered questions. The exact mechanism of rapid plaque progression and triggers of expansive remodeling as well as the role of WSS in these processes is unclear. While, it is obvious that peak WSS increases with advanced plaque progression as a result of a narrower lumen [17], it is very well possible that high WSS has distinct effects on plaque progression and arterial remodeling during different phases of plaque development (early vs. advanced plaques). In one study in patients with non-obstructive coronary artery disease, two-third of segments within large plaques (plaque burden ≥40%) showed high WSS, while only 4% of these segments showed low WSS. In addition, there was a significant linear relationship between higher WSS and higher plaque burden only in larger plaques (plaque burden ≥ 46%) [11]. In the carotid circulation, ulceration of carotid plaques, visible on angiography or on pathological examination, was seen most often in the upstream part where WSS was highest [18] and the inflammatory burden was severe [15]. In the previously mentioned longitudinal study of human coronary arteries, segments with high WSS, which showed longitudinal transformation to vulnerable phenotype, had sufficient plaque burden (45.5±15.9%) at baseline to cause blood flow acceleration and elevated WSS without being flow limiting (as determined by fractional flow reserve) [9]. On one hand, it is believed that expansive remodeling is an adaptive response to elevated WSS to restore the WSS to physiological range and preserve the lumen. On the other hand, when inward progression of the plaque starts, subsequent plaque enlargement and lumen narrowing result in abnormally high values of WSS. It is possible that while some arteries manage to restore WSS to physiological values through expansive remodeling, the others fail and therefore continue having high WSS and expansive remodeling, possibly resulting in rapid plaque progression.

In general, the current literature on high WSS is limited due to small number and heterogeneity of human studies using different study settings (coronary vs. carotid arteries), severity of disease, definitions and methods of assessment of plaque composition (virtual histology intravascular ultrasound vs. magnetic resonance), and

methods of calculation and cutoffs for high WSS. Studies mainly reported the association between high WSS and plaque geometrical determinants and compositions; and the mechanism at microscopic levels, including cellular, molecular and genetic levels, has been least investigated. Moreover, other factors, e.g., intraplaque mechanical stimuli, may also contribute to the plaque development, including IPH formation and development. It has been shown that intraplaque structural stress and strain are important determinants associated with IPH development and aging [19-21].

Despite of the unclear pathological role of mechanical stimuli in the development of IPH, it is clear that IPH together with fibrous cap rupture are the most important features indicating plaque vulnerability [22]. The development of IPH poses an immediate and long-term promoting effect on plaque progression [23]. It appears to alter the biology and natural history of atherosclerosis by contributing to the deposition of free cholesterol, macrophage infiltration, and enlargement of the necrotic core [2]. Therefore, the study by Tuenter et al. provides us with more evidence in favor of the role of high WSS in plaque vulnerability [8]. With the recent interest in high WSS, several experimental and human studies are underway which will hopefully shed light on our understanding of the interplay between WSS and plaque development.

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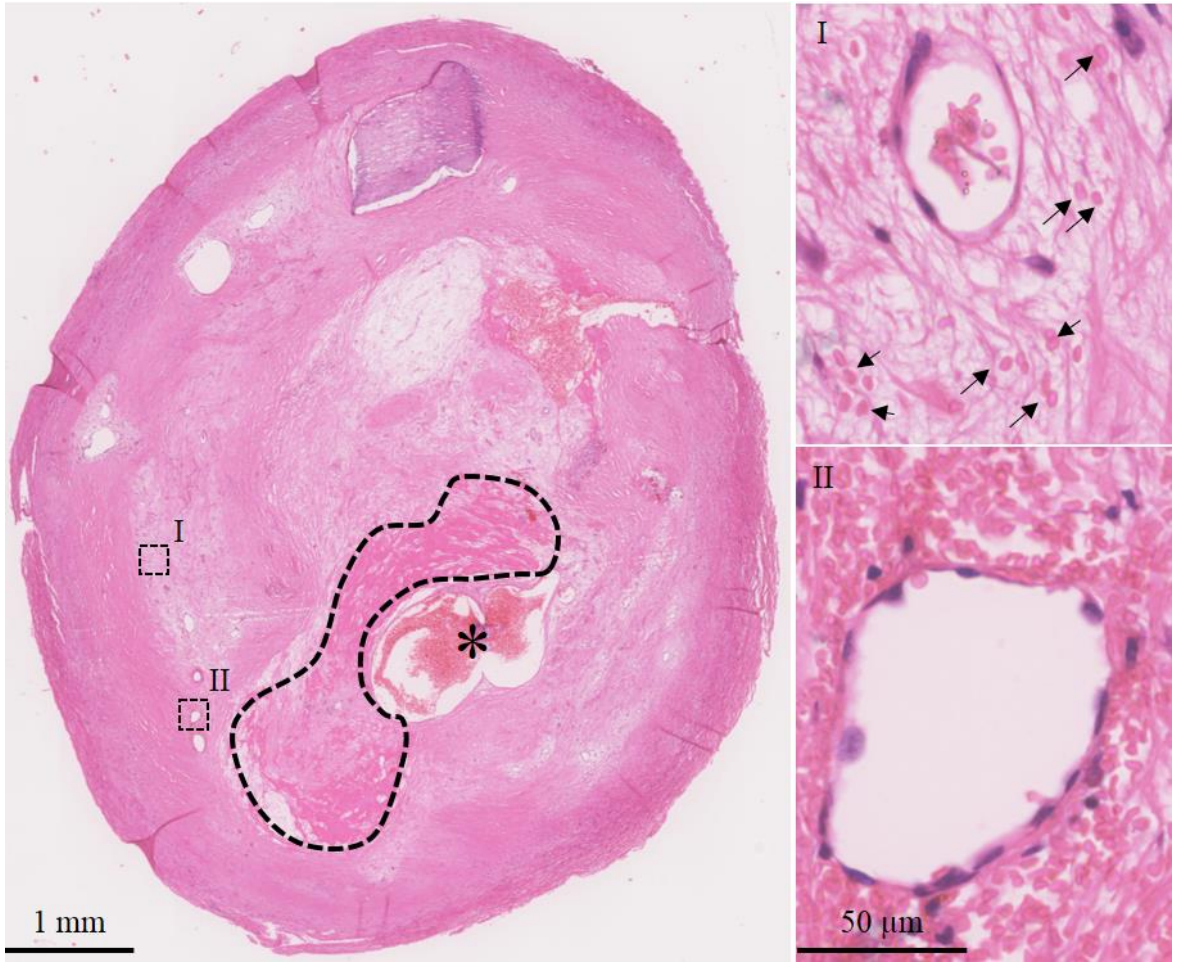
Figure 1. A histological (H&E stain) slice showing detailed structures within a carotid atherosclerotic plaque (I and II show leaking neovessels with red blood cells nearby; arrows in I point to red blood cells; a thrombus attached to the ruptured site is enclosed by a dash line; the main lumen is marked by an asterisk)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