Flow-Dependent Remodeling of Small Arteries
The Stimuli and the Sensors Are (Still) in Question
Akos Koller

From the embryonic state to the end of life, the elements of the circulatory system are exposed to hemodynamic forces associated with the circulation of blood. Various levels of intraluminal (transmural) pressure and wall shear stress represent the natural environment for the tissues of the vascular wall. Physiological or pathological changes in the level of these forces elicit active responses in the cellular and noncellular elements of the vascular wall. In the short-term, vessels may change their functional diameter, whereas, if the hemodynamic forces are altered chronically, this results in morphological changes of the wall, indicated by changes in vessel diameter and wall thickness, frequently termed remodeling, aimed at minimizing the effect of altered hemodynamic forces on the vascular wall.

Pressure-Induced Remodeling of Vessels
A change in intraluminal pressure was the first to be recognized widely as a potential stimulus for functional or morphological changes in vessel diameter.1–3 Indeed, vascular remodeling was recognized as an important factor in the stable increase in peripheral resistance in hypertension, a disease in which the intraluminal pressure is elevated.1–4 There are ample original publications and reviews on this subject.1–4 The present editorial focuses on the remodeling of vessels that are initiated by a change in blood flow.

Flow-Dependent Remodeling of Vessels
Early Findings on the Effects of Chronic Alterations of Blood Flow
In 1893, Thoma summarized, with great insight, his own and other investigators’ ideas describing the relationship between blood flow and vascular dimensions. He posited that growth of the “cross-diameter” of vessels was dependent on the velocity of blood flow. Recklinghausen (1883) and Nothnagel (1889) drew similar conclusions, namely, that it is not an increase in pressure, but rather an increase in flow velocity, which brings about the development of widened or new collateral blood vessels. Later Kamiya and Togawa demonstrated in carotid arteries that flow/wall shear stress elicits remodeling,5 whereas in the mesenteric circulation in vivo it was demonstrated that the magnitude of vessel remodeling is directly dependent on the duration of flow elevation.6 These studies provided strong evidence for the idea that the structure and components of vascular tissues are likely to be determined to a great degree by the hemodynamic forces imposed on them.

Recent Findings on Flow Dependent Remodeling
Because the inner layer of blood vessels is exposed directly to blood flow–related forces, it was logical to assume that flow dependent remodeling is initiated by endothelial mechanisms.7,8 Several in vivo studies, in which mesenteric arteries were exposed to long-term high, low, or normal blood flow by alternatively ligating the arteries established this idea.9–11 These studies found that after 2 to 4 weeks, high flow induced outward, whereas low flow induced inward remodeling.9–11 The amplitude of the change in blood flow and the corresponding arterial remodeling showed a close correlation.10

Potential Role of Extracellular Matrix Transglutaminases in Flow-Dependent Remodeling
In Vitro Studies
The idea that the extracellular matrix bears most of the forces acting on the vascular wall12 stimulated investigations on the role of extracellular matrix–related mechanisms in flow-dependent remodeling of small arteries.13 A role for elastin, collagen, and other components of wall matrix has been envisioned. Based on in vitro studies on cultured vessels Bakker et al proposed a novel alternative mechanism; namely, they proposed that tissue transglutaminases (tTG), a family of cross-linking enzyme, contribute to the inward remodeling of small arteries when flow decreases.14 Activation (constriction) of pressurized isolated arteries with endothelin-1 or exposure to exogenous transglutaminase resulted in inward remodeling, which was blocked by tTG inhibitors.14 This effect of exogenous tTG was inhibited by addition of a nitric oxide (NO) donor, suggesting that NO, also known to be released in response to acute increases in flow,15 prevents inward remodeling by inhibiting tTG.14 Extracellular-matrix assembly and other important biological processes, such as blood coagulation, are dependent on the rapid generation of covalent cross-links between proteins16 catalyzed by transglutaminases, resulting in supramolecular structures with extra rigidity. There are transglutaminases that function as molecular switches in cytoskeletal scaffolding and modulate protein–protein interactions,16 and thus may serve as “tightening glue” in biological materials.17 A review by Langille and Dajnowiec detailing the molecular
mechanisms of tissue transglutaminases potentially involved in remodeling has been recently published.18

In Vivo Studies
In this issue of Circulation Research,19 Bakker at al aimed to confirm their in vitro findings in in vivo conditions. They performed elegant and novel experiments, which provided some unexpected findings. To elucidate the role of tTG in low flow-induced remodeling they imposed a change in blood flow in the parallel network setting of the mesenteric arterial bed10,11 of wild-type (WT) and tTG-null mice. Vessels of WT mice exposed to 2 days of low blood flow showed inward remodeling, which was absent in arteries from tTG-null mice.19 Importantly, they also found that vessels exposed to high blood flow showed similar outward remodeling in WT and tTG−/− mice suggesting no role for tTG in outward remodeling.19 More surprisingly, however, they found that after continued low blood flow for 7 days, vessels of tTG-null mice showed inward remodeling and reduced distensibility similar to those of WT mice19 and stained positively for transglutaminase factor XIII in arteries of tTG-null (and WT) mice.

Another unexpected finding was the observation of the accumulation of adventitial monocytes/macrophages in vessels exposed to low blood flow in tTG-null mice. Because elimination of peritoneal macrophages with liposome-encapsulated clodronate reduced both the expression of factor XIII and inward arterial remodeling they concluded that adventitial monocytes/macrophages are a source of factor XIII in tTG-null mice, which represent an alternative mechanism to elicit delayed (after 7 days) inward remodeling when tTG is (genetically) absent.19 Potential scenarios for flow-induced remodeling of small arteries are depicted in the Figure. However, many intriguing questions remain to be answered.

Controversies Regarding the Wall Elements
Bakker at al suggest that turnover of elastin, collagens, and other wall matrix components significantly contributes to remodeling.19 Yet, the nature and importance of matrix alterations during resistance artery remodeling are still elusive, partly because of the low density of this material in the wall of small arteries.20 Even studies in large arteries (known to have more matrix components) strongly suggest that marked flow-related inward or outward arterial remodeling can proceed without significant modifications in the arterial collagen and elastin contents.21 Flow-induced inward or outward remodeling in mesenteric arteries is associated with SMC turnover and dedifferentiation,22,23 when SMCs are more prone to proliferate, migrate, and synthesize and degrade their matrix24 and thus could contribute substantially to remodeling.

Controversies Regarding the Stimuli and Sensors
Changes in diameter of vessels, whether functional or structural, are considered to minimize the mechanical force acting on the vessel wall.7,25 Thus, it is important to specify the force(s) (or factors) that could be the stimuli for “low flow-induced” remodeling. In general, it is assumed that whenever flow changes, wall shear stress (WSS) changes proportionally in the same direction. This assumption however is not always necessarily true. This can be seen from the following equations deriving from the Hagen-Poiseuille law (where \( \eta \) is viscosity of fluid [blood], \( Q \) is flow, \( r \) is radius, \( v \) is velocity):

\[
WSS = 4\eta \times \frac{Q}{r^2}, \text{or } WSS = \eta dv/dr
\]

For example, a decrease in blood flow or viscosity in the presence of constant diameter decreases WSS. In this condition blood flow decreases due to the decreased velocity of blood. If however, both flow velocity and diameter (2\( r \)) decrease, WSS may not change, and so on. Thus, it is important to know which parameter(s) changed and what changed first. Experimental evidence shows that an increase in viscosity or flow (velocity) (in the presence of constant diameter) increases WSS, which stimulate the endothelium to release factors resulting in dilation and a consequent decrease in WSS.7,25 One can assume the opposite as well. In many conditions, however, it is difficult to ascertain that WSS is the stimulus for change in the diameter of vessels or remodeling;
especially, because (in contrast to flow) WSS cannot be directly measured in blood vessels.

In the studies of Bakker et al the ligated branch is designated as a low flow segment by the authors, yet it is likely that flow declines close to zero, and consequently WSS is likely to be minimal (see supplemental Figure IA, Bakker et al) and the level of intraluminal pressure is also unknown. The latter is important because in in vitro studies of Bakker et al presence of pressure seemed to be also a requisite for low flow-induced remodeling. Moreover, the second branch designated as normal flow is likely to receive higher than normal blood flow, because this branch is coupled in a parallel manner to the arterial circulation, thus flow should increase in this branch a well, not just in the branch adjacent to the ligated one. In addition, because of the active feedback mechanisms between diameter and hemodynamic forces continuous measurement of pressure, flow, diameter, wall thickness, and calculation of WSS would be necessary to ascertain the chronically prevailing level of WSS (and wall tension). This, of course, is easier said than done. It should also be mentioned that “flow” might also be sensed by the vascular or parenchymal tissue by mechanisms sensitive to the mass transport of molecules. These mechanisms are difficult to exclude during various experimental interventions or in pathologic conditions (Figure).

Perhaps the most intriguing question is how adventitial monocytes/macrophages can “sense” or be influenced by flow or shear stress. If not shear stress, then what is the stimulus for the release of factor XIII from monocytes/macrophages during low flow conditions? Do they originate from the peritoneum or from the lumen of vessels? In this context the findings of Walpola et al are particularly interesting by showing that reduced flow in the rabbit carotid artery segment resulted in a decrease in shear stress from \(\approx 12\) to \(\approx 3.3\) dynes/cm\(^2\) and increased the number of monocytes attached and migrating across the endothelial cells. By contrast, presence of flow/shear stress reduced endothelial adhesiveness for monocytes, an effect that is largely attributable to flow-stimulated release of NO and which decreased markedly the level of vascular cell adhesion molecule-1 (VCAM-1) expressed on the endothelial cell surface. One would also like to know whether during low flow the reduced level of NO leads to inward remodeling via upregulation of tTG or via promoting monocyte/macrophage activation/recruiting, or both (Figure). Are there macrophages around the vessels exposed to low flow in WT mice? Among other factors that may influence trafficking of monocytes/macrophages in tTG/\(−/−\) mice is the ligation of vessels, which could activate mechanisms independent of hemodynamic forces, such as vascular or parenchymal ischemia. Furthermore, one may also entertain the idea that a reduced level of NO may indirectly increase the level of reactive oxygen species, and thus their role in inward remodeling should also be considered.

Interestingly, a previous mathematical model study by van Bavel’s group predicted that shear stress is not sufficient to control growth of the vascular network. Theoretical work of Pries at al on information transfer in vascular networks predicted that although shear stress–mediated coupling is the main mechanism, adaptation of vascular network stability and vascular structure are also dependent on other mechanisms, such as input of tissue metabolites and conducted signals along the wall. Nevertheless, the previous and present studies of Bakker at al should remind us that ideas developed in vitro need to be tested in vivo, because they may reveal mechanisms that are not present in vitro.

**Concluding Remarks**

Adaptation of living cells to the ever-changing environment is one of the basic necessities to maintain life. The surprising and provocative findings of Bakker at al merit serious consideration, but like many other good investigations, they open up more avenues of investigation than they answer questions. The excellent work of Bakker at al will stimulate continuous interest in solving the puzzle of vascular remodeling. Nevertheless, in addition to morphological and signal transduction studies, experiments measuring the functional consequences of remodeling, such as myogenic and shear stress–dependent responses, need to be characterized to better understand the reasons for remodeling of vessels.

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**References**


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