Vascular Remodeling

Hemodynamic and Biochemical Mechanisms Underlying Glagov’s Phenomenon

Vyacheslav A. Korshunov, Stephen M. Schwartz, Bradford C. Berk

Abstract—An important concept for vascular remodeling, termed Glagov’s phenomenon, is that arteries remodel to maintain constant flow despite increases in atherosclerotic lesion mass. Although Glagov’s phenomenon was originally described only for the case of arterial remodeling in response to growth of atherosclerotic plaques, experimental and clinical observations indicate that blood flow properties influence remodeling after angioplasty, hypertension, and flow diversion as well as atherosclerotic plaque progression. This review attempts to define Glagov’s observation in terms of the physical parameters of blood in conduit arteries that must determine the remodeling response. Next we review experiments that have begun to identify specific molecules that influence vascular remodeling and therefore may serve as mediators for the phenomena. More comprehensive analyses of the specific molecular pathways in the vessels that determine constant flow may provide new therapeutic approaches to regulate vascular remodeling. (Arterioscler Thromb Vasc Biol. 2007;27:1722-1728.)

Key Words: vascular remodeling ■ Glagov’s phenomenon ■ shear stress

In 1987 Glagov reported the surprising finding that atherosclerotic arterial lumen narrowing is not simply the result of enlargement of atherosclerotic lesions.1 He and several colleagues found instead that arteries remodel over a large range of changes in wall mass, increasing the external diameter in a manner that allows preservation of the arterial flow. This ability of arteries to adapt is central to most arterial diseases. Like atherosclerotic coronary artery disease, peripheral vascular disease and systemic hypertension can be thought of as failure of the arterial wall to maintain the appropriate lumen size needed to permit normal blood flow. It was recently suggested that the inability of vessels to remodel appropriately is a form of “vascular failure” similar to the well established syndrome of cardiac failure.2 A definition of failure must begin with a description of the normal mechanisms that allows arterial walls to adapt to physiological demands.

Physical Laws That Govern the Interactions Between Blood and Arterial Wall

Blood flow through the large conduit arteries is governed by physical laws. These laws depend on laminar flow, dictated by Reynolds number, with the parameters controlling blood flow described by Poiseuille’s law, and the forces acting on the wall by LaPlace’s law. The combination of Reynolds’s number and the two laws constrains the biological possibilities. For example, the Reynolds number (NR) predicts the occurrence of turbulent flow when NR$\leq$Prvd/η; based on fluid density (ρ, kg/L), flow velocity (V, m/sec), vessel diameter (D, cm), and blood viscosity (η, g/cm/s). Values of NR$<$2000 predict laminar flow whereas values of NR$>$3000 predict that turbulence will usually exist. Blood flow in conduit arteries is nonturbulent, except focally such as may occur at bifurcations.3 Similarly, the mechanical properties of the proteins comprising the vessel wall determine the wall thickness values in the LaPlace equation.

Assuming circular lumens with parabolic velocity profiles, one can determine the dragging frictional force exerted by blood on the artery wall using Poiseuille’s law termed shear stress (τ, dyne/cm²): $\tau=4\eta Q/P_{\text{lumen}}^3$, where η is blood viscosity (g/cm/s), Q (cm³/s) is volume blood flow, and $P_{\text{lumen}}$ (cm) is lumen radius. Because Q is proportional to the third power of $P_{\text{lumen}}$, even small changes in lumen size greatly affect shear stress. LaPlace’s law ($T=Pr$) postulates that tension (T) is proportional to pressure (P) and $P_{\text{lumen}}$. The wall tensile stress ($T=Pr_{\text{lumen}}/h$) is directly proportional to P and $P_{\text{lumen}}$ and inversely related to wall thickness (h). In addition to flow, wall tensile stress, and shear stress, the same parameters will determine rates of fluid transport into the vessel wall.4 In turn, remodeling must depend on transduction into biochemical signals of shear stress, thermal transfer, wall tension, or fluid transport, the physical results of the forces acting on the arterial wall.5 Importantly, the parameters in the latter equations are regulated within a very narrow range in all mammals.

© 2007 American Heart Association, Inc.

Arterioscler Thromb Vasc Biol. is available at http://www.atvbaha.org

DOI: 10.1161/ATVBAHA.106.129254
suggesting strong evolutionary pressure and physiological optimization. In particular, levels of shear stress are constant (≈20 dyne/cm²) especially in large arteries under normal physiological conditions.5

Unfortunately the terminology used to describe remodeling is controversial and inconsistent.6,7 We define the external radius (rₑₓ) as the radius that describes the extent of the external elastic lamina. Wall thickness (h) in the Laplace’s equation is defined as external radius minus lumen radius (rₑₓ − rₗum). This usage is similar to that proposed by Mulvany et al8 for vascular remodeling of resistance arteries in hypertension, although the terminology remains an area of active discussion.6,7

Glagov’s Phenomenon: A Characteristic Feature of Arterial Remodeling

Atherosclerosis

Although conventional wisdom, before the 1980s, held that atherosclerosis narrows vessels by encroachment of the growing plaque into the lumen, Glagov and colleagues1 found that the lumen area of atherosclerotic human coronaries remained constant until the percent stenosis exceeded 40% (Figure 1B). At this point lumen diameter decreased, resulting in a restriction in flow (Figure 1B, right). Glagov’s postmortem study in humans was consistent with prior data obtained in animals with experimentally induced atherosclerosis.9,10 In particular, Bond and colleagues9 noted that cynomolgus monkey fed an atherosclerotic diet for 3 years exhibited not only greater lesions, but also much larger coronary internal elastic lamina (IEL) compared with animals on control diet. Armstrong et al10 further showed that iliac-femoral arteries enlarge with preserved lumen in atherosclerotic rhesus and cynomolgus monkeys. More recently, Glagov’s phenomenon has been observed in atherosclerotic mice.11

Vascular Injury and Restenosis

Whereas the description of the phenomenon was based on observations in atherosclerosis, we propose that the same phenomenon is observed in a wide range of pathophysiological conditions associated with vascular remodeling. For example, coronary arteries with transplant arteriopathy exhibit compensatory increases in rₑₓ that preserve lumen diameter despite significant thickening of the affected vessel wall.12 A murine model of primary atherosclerosis and angioplasty with intimal hyperplasia also showed increased rₑₓ while maintaining rₗum.13

Glagov’s phenomenon is also observed in vascular injury and restenosis (Figure 1C). Specifically, the failure of a narrowed atherosclerotic vessel to remain open after mechanical dilatation is termed “restenosis”. Contrary to the general assumption that a mechanically dilated lumen is narrowed because of growth of an intima, data show that stenosis is attributable to restoration of the rₗum that existed before the mechanical dilation. Thus the failure of the vessel to enlarge after mechanical dilatation might have been predicted based on the general operation of Glagov’s phenomenon.14,15 As shown in Figure 1C (left, no restenosis), as shown in the Multivitamins and Probucol (MVP) study, probucol treatment (compared with placebo or antioxidant vitamins, Figure 1C, right, restenosis) prevented lumen loss. However, there was no difference in rₑₓ − rₗum (measured as intima-media thickening) between the two groups (details are in legend for Figure 1C). The difference in lumen was completely accounted for by increases in rₑₓ, sometimes called “outward remodeling” with probucol, whereas “inward remodeling”, that is a decrease in rₑₓ occurred with placebo. Long term follow-up studies of vessels after PCTA showed that the major mechanism of remodeling followed restenosis is a failure of rₑₓ to increase.16 Again, this is seen in animal models. Courtman et al17 showed no loss of lumen size in

Figure 1. Scheme for vascular remodeling. A, Normal artery. White arrow points to physiological remodeling, black arrow to pathophysiological remodeling. B, Progression of atherosclerosis causes lumen narrowing when stenosis exceeds 40% (adapted from1). C, Vascular injury after percutaneous transluminal angioplasty (PTCA) causes constrictive remodeling with decreased vessel size (restenosis), whereas probucol treatment promoted outward vessel remodeling and prevented lumen narrowing (No restenosis: −0.2 mm in probucol versus −1.2 mm in placebo, a 6-fold inhibition of restenosis). However, vessel wall increased equally (0.3 mm) in both groups.14,15
rabbit aorta after a single angioplasty. A repeat angioplasty narrowed the lumen even though there was no further increase in intima mass. This effect could be blocked with an inhibitor of fibrin formation. Hence, in this model, failure of “outward remodeling” resulted from pathological deposition of fibrin in the vessel wall rather than an increase in intima formation. These studies suggest that the Glagov’s phenomenon is applicable to vascular injury as well as atherosclerosis.

**Hypertension**

Mulvany et al\(^8\) proposed terminology to classify changes in hypertensive vessels based on changes in lumen diameter (inward or outward) and wall area (increased = hypertrophic, decreased = hypotrophic, no change = eutrophic). The most common hypertensive change in the small caliber resistance arteries is a decrease in lumen diameter with no change in wall area (\(r_{\text{int}} - r_{\text{lumen}}\)) but a decrease in \(r_{\text{ext}}\). In his terminology it is called eutrophic inward remodeling. This change may be very important in establishment of elevated blood pressure. For example, a reduction in \(r_{\text{ext}}\) accounted for 76% of the decrease in lumen diameter in the stroke-prone hypertensive rabbit aorta after a single angioplasty. A repeat angioplasty narrowed the lumen even though there was no further increase in intima mass. This effect could be blocked with an inhibitor of fibrin formation. Hence, in this model, failure of “outward remodeling” resulted from pathological deposition of fibrin in the vessel wall rather than an increase in intima formation. These studies suggest that the Glagov’s phenomenon is applicable to vascular injury as well as atherosclerosis.

**Hemodynamic Factors in Pathophysiologic Conditions**

Among the physical factors listed above as potential controls for remodeling, shear stress has been most studied.\(^5,25-27\) Measurements of site-specific vessel geometry, flow, and plaque burden using combined imaging modalities have enabled spatially accurate correlations between local shear stress and plaque progression in human coronary arteries.\(^26\) Even in healthy subjects, carotid intima-media thickening (IMT) is inversely related to carotid shear stress.\(^28\) In the case of atherosclerotic human coronary arteries, at least two processes appear to maintain a normal lumen size. In the presence of high shear stress (\(\tau > 38 \text{ dyne/cm}^2\)) arteries remodeled by decreasing plaque area and increasing lumen without changes in vessel size measured by \(r_{\text{ext}}\). In arterial sites with low shear stress (\(\tau < 9 \text{ dyne/cm}^2\)) lumen was maintained despite an increase in plaque size, by an increase in \(r_{\text{ext}}\). At intermediate values of shear stress (9 < \(\tau < 38 \text{ dyne/cm}^2\)) both processes occurred.\(^26\) While these sophisticated studies have been performed in a limited number of patients, it appears that about 60% of arteries adhere to Glagov’s phenomenon and compensate appropriately. The remaining 40% of vessels fail to remodel outward or exhibit a decrease in \(r_{\text{ext}}\).

After balloon angioplasty of normal carotids in the rat, low blood flow promoted decreases in lumen caliber attributable to eutrophic inward remodeling, ie, decreases in both \(r_{\text{ext}}\) and \(r_{\text{lumen}}\) but no effect of flow on \(r_{\text{int}}\) as shown in Figure 1C.\(^29\) Experiments on external iliac arteries of atherosclerotic Yucatan minipigs showed that reduction in \(r_{\text{int}}\) was controlled by both shear stress and wall stress but not wall mass.\(^30,31\) These animal models may not be very useful in the human condition because recent clinical observations demonstrated that \(r_{\text{ext}} - r_{\text{lumen}}\) negatively correlated with shear stress in the coronary arteries of patients followed for 6 months after PCTA.\(^32\)

Heart rate and pulse pressure are the two key factors in the remodeling of the large arteries in hypertension.\(^20,21,33\) Giannattasio et al\(^34\) showed in humans that arterial distensibility significantly decreased as heart rate was increased by a pacemaker. Other studies have suggested that increases in pulse pressure are most important for increases in \(r_{\text{int}}\) and \(r_{\text{ext}} - r_{\text{lumen}}\) of the carotid artery in hypertension,\(^26\) because the change in pulse pressure correlated better than change in mean blood pressure with reduction in IMT, \(r_{\text{ext}} - r_{\text{lumen}}\), during long-term antihypertensive treatment.\(^30\)

**Identification of Specific Biochemical Pathways**

The mechanisms responsible for flow-dependent remodeling have been most frequently studied in animal models, in which the carotid arterial tree is partially or completely ligated. In the partial carotid ligation model, the left external and internal carotid arterial branches are ligated so that blood flows via the patent occipital artery. Flow via the common carotid is reduced by \(\approx 90\%\) and increased by \(\approx 50\%\) in the contralateral carotid.\(^35-38\) As predicted by the importance of shear stress in vascular remodeling, there is an increase in \(r_{\text{int}}\) in the high flow carotid with outward vessel remodeling (increased \(r_{\text{ext}}\)). Remodeling of the low flow common carotid in this model is similar to Glagov’s phenomenon.\(^27\) In particular, FVB/NJ and SJL/J exhibited extensive increases in carotid \(r_{\text{ext}} - r_{\text{lumen}}\) that was compensated by increased \(r_{\text{ext}}\) (Figure 2). Although the single gene transgenic mouse approach (discussed below) has yielded important insights, developing physiological models that can be subjected to genomic and
proteomic analyses will be necessary, because flow-dependent vascular remodeling involves multiple cell types and processes. Our recent observations in 5 inbred mouse strains emphasized the role of genetic factors in the ability of carotid arteries to follow phenomena in partial ligation model.\(^{26}\) First, consistent with Glagov’s data,\(^1\) there was a significant correlation between increased IMT and increased \(r_{\text{tot}}\) (measured by EEL in Figure 2A). Second, maintenance of lumen area occurred until the stenosis (%stenosis/\(H100\)) exceeded 55%.\(^ {27}\) This transition point at 55% is similar to Glagov’s observation, although the transition point for lumen decrease in mice was higher than in humans (~40%).\(^ {1}\) The higher value in mice may be attributable to differences in species, artery types (carotid versus coronary), and the fact that in humans coronary medial changes were excluded from the analysis (\(r_{\text{tot}}=\text{IEL}\)).\(^ {1}\) Nevertheless, mouse carotid \(r_{\text{tot}}-r_{\text{lumen}}\) and \(r_{\text{tot}}\) were similar to human coronary remodeling in vivo.\(^ {26}\) Third, there were also significant strain-dependent differences in the remodeling index (measured as the slope of \(r_{\text{tot}}-r_{\text{lumen}}\)). For example, FVB/NJ mice increased \(r_{\text{tot}}\) twice as much as SJL/J mice and C3H/HeJ mice, for the same increase in IMT (Figure 2B).

Despite the obvious limitations of the total carotid ligation model in regards to presence of flow, it has been more frequently used than the partial ligation model in transgenic mice. Total ligation produced dramatic neointima formation in arteries that is complicated by thrombotic and inflammatory changes beyond the scope of this review.\(^ {39}\) Thus, we think that the total ligation model represents a model for “vascular failure” of physiological adaptation, such as Glagov’s phenomenon. However, there are likely common genetic mechanisms underlying intima formation after cessation of flow, because the same mouse strains (SJL/J and FVB/NJ) exhibited largest neointima.\(^ {40}\) Yet, fundamental differences between these 2 models was shown by the opposite intima-to-media ratio, ie, the largest intima formation after total ligation was in FVB/NJ, whereas after partial ligation was found in SJL/J.\(^ {27,40}\) Genetic differences also appear when the intima response of the mouse carotid following wire injury is studied,\(^ {41}\) suggesting the presence of certain genes that determine intima formation in both flow dependent and flow independent responses to injury.

Because the majority of studies on transgenic mice have been focused on the mechanisms of neointima proliferation using complete ligation, a model of “vascular failure” of flow, we cannot directly extrapolate them to Glagov’s phenomenon. However, 9 candidate mediators (of >30 genes studied so far) may be involved in physiological adaptation based on their contribution to maintenance of \(r_{\text{tot}}\) in a failing carotid (Figure 3). The center point labeled “X” in Figure 3 represents the baseline physiological relationship between vascular size and thickness. In response to genetic manipulation, several phenotypic changes in this relationship occur. We discuss the 4 responses observed to date: (1) reduction of \(r_{\text{tot}}\) with increases in \(r_{\text{tot}}-r_{\text{lumen}}\) identify “reducing” genes (nNOS\(^{−/−}\), P2X type ATP receptors \(^{−/−}\), vimentin \(^{−/−}\)); (2) reduction of \(r_{\text{tot}}\) without \(r_{\text{tot}}-r_{\text{lumen}}\) changes identify “reducing” genes (iNOS\(^{−/−}\), TL4-\(^{−/−}\)); (3) reduction of \(r_{\text{tot}}\) with decreases in \(r_{\text{tot}}-r_{\text{lumen}}\) identify “augmented” genes (matrix metalloproteinase [MMP]-9\(^{−/−}\), t-ACE\(^{−/−}\), dopamine β-hydroxylase); and, (4) overexpression of p22\(^{\text{phox}}\) further increases \(r_{\text{tot}}\) with increases in \(r_{\text{tot}}-r_{\text{lumen}}\).

Several pathways identified by genetic manipulation appear particularly important in modifying the relationship between vascular size \((r_{\text{tot}})\) and thickness \((r_{\text{tot}}-r_{\text{lumen}})\) after flow reduction (Figure 3). First, nitric oxide (NO) is one of the crucial molecules involved in neointima formation after total ligation.\(^ {42−44}\) However, NO synthase (NOS) isoforms have different effects on remodeling induced by flow cessation. NO derived from eNOS inhibits intima formation without effect on \(r_{\text{tot}}\).\(^ {42,43}\) However, NO derived from iNOS is required for the increase in \(r_{\text{tot}}\) without effect on \(r_{\text{tot}}-r_{\text{lumen}}\).\(^ {42}\) Furthermore, NO derived from nNOS is required for increases in \(r_{\text{tot}}\) and decreases in \(r_{\text{tot}}-r_{\text{lumen}}\).\(^ {44}\) Second, studies in P2XR4\(^{−/−}\) mice (ATP-gated P2X4 ion channel, expressed on endothelial cells) demonstrated that these ion channels were also required for NO production and remodeling.\(^ {45}\) Third, a cytoskeletal protein, vimentin, appears to be critical for the increase in \(r_{\text{tot}}\) and decrease in \(r_{\text{tot}}-r_{\text{lumen}}\) after cessation of blood flow.\(^ {46}\) Finally, activation of the toll-like receptor-4 (TLR-4) seems to be a powerful regulator of the in \(r_{\text{tot}}\) without effect on \(r_{\text{tot}}-r_{\text{lumen}}\) after total ligation.\(^ {47}\)

On the other hand, several genes are important for increases in both \(r_{\text{tot}}\) and \(r_{\text{tot}}-r_{\text{lumen}}\) (Figure 3). First, experiments using total ligation model showed a key role for metallopro-
teinase 9 (MMP-9) that regulated both $r_{es}$ and $r_{es}-r_{amu}$.48 Using a partial ligation model in C57Bl/6J and FVB/NJ mice49 we found that increased expression of plasminogen activators tissue-type plasminogen activator (t-PA) and u-PA correlated significantly with increased IMT. Expression of MMP-2, MMP-9, and TIMP-2 also increased, but did not correlate with remodeling. Second, arterial angiotensin II and macrophage migration inhibitory factor (MIF) were shown to be markedly increased in carotids from SJL/J mice53. Recent clinical and genetic epidemiological studies suggest that MIF and IL-18 may contribute to human pathology.54–58 These data suggest that the ability to increase $r_{es}$ is termed “reducing” genes, whereas those that enhance the ability to increase $r_{amu}$ are termed “augmenting” genes. Arrows point in the direction of changes based on transgenic phenotypes (see details in text).

The role of inflammation and white blood cells in vascular remodeling has become increasingly apparent. Activation of the toll-like receptor-4 (TLR-4) seems to be critical for flow-induced remodeling, because t-ACE and dopamine $\beta$-hydroxylase knockout mice exhibited decreases in both $r_{es}$ and $r_{es}-r_{amu}$ 50,51. Finally, one study suggested that redox state can affect low flow remodeling because over-expression of p22phox (a critical component of NAD(P)H oxidase) significantly increased both $r_{es}$ and $r_{es}-r_{amu}$ after total ligation.52

The ability of arteries to maintain constant flow and lumen size, $r_{amu}$, in the face of a growing atherosclerotic lesion is also seen in other adaptive responses of the artery wall to injury. When this phenomenon fails to occur the result is stenosis, indicating that failure of the compensatory mechanisms is an important clinical issue. The most likely physical parameter controlling this response is shear stress. Recent studies using genetics, single gene knockout animals, and other experimental systems have begun to identify candidates for both the transduction mechanisms and the target molecules that mediate the remodeling response.

Sources of Funding

Dr. V.A.K. is an AHA Scientist Development Grant awardee (0430267N). This work was also supported by NIH grant HL-62826 to B.C.B.

Disclosures

None.

References

Korshunov et al

Glagov’s Phenomenon and Blood Flow


Vascular Remodeling: Hemodynamic and Biochemical Mechanisms Underlying Glagov's Phenomenon
Vyacheslav A. Korshunov, Stephen M. Schwartz and Bradford C. Berk

Arterioscler Thromb Vasc Biol. 2007;27:1722-1728; originally published online May 31, 2007; doi: 10.1161/ATVBAHA.106.129254

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/27/8/1722

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/