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Effects of Disturbed Flow on Vascular Endothelium: Pathophysiological Basis and Clinical Perspectives

Jeng-Jiann Chiu and **Shu Chien**
Division of Medical Engineering Research, National Health Research Institutes, Taiwan; UST-UCSD International Center of Excellence for Bioengineering, National Yang-Ming University, Taiwan; and Departments of Bioengineering and Medicine and Institute of Engineering in Medicine, University of California, San Diego, La Jolla, California

Abstract

Vascular endothelial cells (ECs) are exposed to hemodynamic forces, which modulate EC functions and vascular biology/pathobiology in health and disease. The flow patterns and hemodynamic forces are not uniform in the vascular system. In straight parts of the arterial tree, blood flow is generally laminar and wall shear stress is high and directed; in branches and curvatures, blood flow is disturbed with nonuniform and irregular distribution of low wall shear stress. Sustained laminar flow with high shear stress upregulates expressions of EC genes and proteins that are protective against atherosclerosis, whereas disturbed flow with associated reciprocating, low shear stress generally upregulates the EC genes and proteins that promote atherogenesis. These findings have led to the concept that the disturbed flow pattern in branch points and curvatures causes the preferential localization of atherosclerotic lesions. Disturbed flow also results in postsurgical neointimal hyperplasia and contributes to pathophysiology of clinical conditions such as in-stent restenosis, vein bypass graft failure, and transplant vasculopathy, as well as aortic valve calcification. In the venous system, disturbed flow resulting from reflux, outflow obstruction, and/or stasis leads to venous inflammation and thrombosis, and hence the development of chronic venous diseases. Understanding of the effects of disturbed flow on ECs can provide mechanistic insights into the role of complex flow patterns in pathogenesis of vascular diseases and can help to elucidate the phenotypic and functional differences between quiescent (nonatherogenic/nonthrombogenic) and activated (atherogenic/thrombogenic) ECs. This review summarizes the current knowledge on the role of disturbed flow in EC physiology and pathophysiology, as well as its clinical implications. Such information can contribute to our understanding of the etiology of lesion development in vascular niches with disturbed flow and help to generate new approaches for therapeutic interventions.

I. INTRODUCTION

Vascular endothelial cells (ECs), which form the inner lining of blood vessel wall with direct exposure to blood flow, serve important homeostatic functions in response to various chemical and mechanical stimuli (87, 111, 125, 337, 485, 573). Besides providing a selective barrier for macromolecular permeability, ECs can influence vascular remodeling via the production of growth-promoting and -inhibiting substances; modulate hemostasis/thrombosis through the secretions of procoagulant, anticoagulant, and fibrinolytic agents;

Address for reprint requests and other correspondence: S. Chien, Dept. of Bioengineering, Univ. of California, San Diego, La Jolla, CA 92093-0427 (shuchien@ucsd.edu).

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mediate inflammatory responses via the surface expression of chemotactic and adhesion molecules and release of chemokines and cytokines; and regulate vascular smooth muscle cell (SMC) contraction through the release of vasodilators and vasoconstrictors (337). Endothelial dysfunction may lead to pathophysiological states that contribute to the development of vascular disorders resulting from atherosclerosis, thrombosis, and their complications (36, 93, 156, 203, 209, 493, 571).

While certain types of hemodynamic forces are essential for physiological functions of the EC under normal conditions, other types can induce endothelial dysfunction by adversely modulating EC signaling and gene expression, thus contributing to the development of vascular pathologies (42, 87, 93, 212, 213, 337, 360, 416, 451, 485, 571, 625), in concert with the risk factors that act on the entire arterial system (e.g., genetics, biochemical factors, living habits, etc.) (220, 253, 641). The possible role of hemodynamic forces in endothelial dysfunction was first suggested by the observation that the earliest lesions of atherosclerosis characteristically develop in a nonrandom pattern, i.e., preferentially at arterial branches and curvatures (or bends) (Fig. 1), where the local flow is disturbed. The disturbed flow pattern includes recirculation eddies and changes in direction with space (flow separation and reattachment) and time (reciprocating flow) (Fig. 2) (16, 39, 68, 69, 108, 111, 183, 186, 189, 190, 207, 210, 216, 217, 292, 311, 339, 393, 406, 416, 454, 492, 494, 502, 513, 534, 535, 545, 590, 595, 644, 645). Recent studies indicate that such disturbed flow and the associated low and reciprocating shear stress induce a sustained activation of a number of atherogenic genes in ECs, e.g., the monocyte chemotactic protein-1 (MCP-1) that induces monocyte infiltration into the arterial wall (86, 87, 256, 257, 265, 337, 520, 523–525) and platelet-derived growth factors (PDGFs) that enhance EC turnover and SMC migration into the subintimal space (309, 361, 616). In contrast, the straight part of the artery, which is generally spared from atherosclerotic lesions, is exposed to sustained laminar blood flow and high shear stress (with a definite direction), with the associated downregulation of atherogenic genes (e.g., MCP-1 and PDGF-BB) and upregulation of antioxidant and growth-arrest genes in ECs (37, 86, 87, 257, 266, 337, 361, 573). These findings suggest that disturbed and laminar flow patterns may induce differential molecular responses in ECs to result in, respectively, the preferential localization of atherosclerotic lesions at arterial branches and curvatures and the sparing of the straight parts of the arterial tree (135, 438). Disturbed flow may also occur in the aortic side of the valvular leaflets, which may regulate valvular endothelial signaling and phenotype that contribute to the preferential susceptibility to lesion development in this region (58, 129, 636). In the venous system, disturbed flow associated with reflux (i.e., retrograde flow) through dysfunctional or incompetent valves, outflow obstruction or stasis, or their combination, may cause venous hypertension, which may induce venous EC dysfunction and inflammation, and consequently result in the development and progression of chronic venous diseases, including varicose veins, deep venous thrombosis, and chronic venous insufficiency (36). Understanding of the effects of disturbed flow on EC signaling, gene expression, structure, and function will help to define the molecular and mechanical bases for the role of complex flow patterns in the development of vascular pathologies such as atherosclerosis, thrombosis, in-stent restenosis, bypass graft occlusion, transplant vasculopathy, aortic valve calcification, and venous valvular incompetence, as well as their clinical complications. Furthermore, such information may lead to the discovery and identification of new disease-related genes and the development of novel therapeutic strategies.

In this article, we provide an overview of the current experimental and theoretical knowledge on the effects of disturbed flow on ECs, in terms of signal transduction, gene expression, and cellular structure and function, as well as clinical relevance and applications. While our main objective is to review vascular endothelial responses to disturbed flow in vivo observed at branch points, curvatures, valve sinuses, and poststenotic regions, we also

discuss in vitro flow channel studies on the responses of cultured ECs to flow patterns without a clear direction versus pulsatile flow with a clear direction. Such in vitro studies allow a more detailed analysis of the molecular and cellular bases of mechanotransduction under these flow conditions that simulate what occur in different parts of the vasculature. We summarize our understanding of the pathophysiological mechanisms of lesion development in regions of disturbed flows that occur naturally in certain vascular niches or evolves following clinical interventions, and discuss their relevance to clinical application and perspectives.

II. HEMODYNAMIC FORCES AND ENDOTHELIAL DYSFUNCTION

This section provides an overview of the fundamental basis of hemodynamic forces acting on the vessel wall and their influences on vascular homeostasis and remodeling, as well as the pathophysiological factors contributing to endothelial dysfunction. These fundamentals help in the understanding of the mechanisms underlying the etiology of lesion development in vascular niches with disturbed flow, and hence the clinical occurrence of disturbed flow and its pathophysiological role to be discussed in section **III**.

A. Hemodynamic Forces, Vascular Homeostasis, and Remodeling of Blood Vessels

Blood vessels are constantly subjected to various types of hemodynamic forces (including hydrostatic pressure, cyclic stretch, and fluid shear stress) induced by the pulsatile blood pressure and flow (Fig. 3). As a monolayer in direct contact with the flowing blood, ECs bear most of the wall shear stress, which is the component of frictional forces arising from blood flow and acting parallel to the vessel luminal surface (125, 192, 337). The magnitude of shear stress in straight vessels can be estimated as being directly proportional to the viscosity of blood and inversely proportional to the third power of the inner radius of vessel (192, 360). Experimental measurements using different methods have shown that in humans the magnitude of shear stress ranges from 1 to 6 dyn/cm^2 in the venous system and from 10 to 70 dyn/cm^2 in arteries (85, 360, 417). The magnitude of shear stress in the normal mouse aorta is much higher (approximately an order of magnitude) than in humans (82, 552), consistent with the concept of allometric scaling that relates structure or function among species of vastly different sizes (224). In vivo observations indicate that increases or decreases in shear stress, rather than the absolute levels of shear stress, play critical roles in vascular homeostasis and remodeling (82, 281, 323, 465, 603). For example, increases in blood flow by constructing an arteriovenous shunt between the common carotid artery and the external jugular vein in dogs cause an initial increase in shear stress in shunted artery, which induces a compensatory expansion of the inner vessel radius of this artery within 6–8 mo to maintain the mean shear stress at the baseline level (281). Unilateral augmentation of femoral arterial flow induced by either acetylcholine administration or arteriovenous shunt elicits dilation with increase in diameter in 18 of 23 dogs, whereas the diameter of the contralateral control artery is not affected (465). Surgical manipulations by ligating the left common carotid artery of young rabbits at 3 wk of ages to increase laminar shear stress in the right carotid artery induce remodeling of this artery over 12 wk to increase the luminal diameter (or inner radius) (152), thus mitigating the increase in shear stress. A study of flow-induced arterial remodeling in rat mesenteric arteries suggests that this response involves the hyperplasia of both ECs and SMCs and an increase in synthesis of connective tissue in the vessel wall (580). The other side of the coin is that a decrease in shear stress resulting from the lowering of blood flow or blood viscosity can induce a decrease in inner radius of the vessel resulting from intima-media hyperplasia or wall hypertrophy (306, 307, 323, 375, 549). A 70% reduction in the rate of blood flow in the common carotid artery of rabbits caused a 21% decrease in the diameter of this artery within 2 wk (323). This decrease in arterial diameter induced by flow reduction is endothelium dependent and not relieved by

the vascular SMC relaxant papaverine, suggesting the occurrence of structural changes in the vessel wall rather than an increased vascular SMC contraction (323). Reduction in shear stress in a ligated unilateral common carotid artery in mice results in remodeling and formation of neointima hyperplasia containing BrdU-positive and SMα-actin-positive cells (481). Such positive remodeling induced by increased shear stress (i.e., eutrophic vessel enlargement) and negative remodeling induced by decreased shear stress (i.e., hypertrophic vessel narrowing) are also important during normal embryonic and postnatal growth and use-dependent hypertrophy or atrophy of tissues (471). The signaling molecules involved in the flow-induced arterial remodeling include fibroblast growth factor-2 (549), adrenergic agents (170), nitric oxide (NO) (639), caveolin-1 (639), tissue transglutaminase [a calcium-dependent enzyme that induces protein cross-linking via ε-(γ-glutamyl)lysine bonds] (20), G protein-coupled receptors (572), receptor tyrosine kinases (572), Axl (a receptor tyrosine kinase whose ligand is growth arrest-specific protein 6) (307), ATP-gated P2×4 ion channel (632), heparin-binding epidermal growth factor-like growth factor (a potent vascular SMC mitogen) (572, 649), and cyclophilin A [a 20-kDa chaperone protein secreted from vascular SMCs in response to reactive oxygen species (ROS) to stimulate their proliferation and migration] (501). The compensatory arterial response to changes in shear stress during arterial remodeling requires an intact, functional endothelium and its ability to undergo adaptive adjustments in structure and function in response to shear stress alterations (206, 323, 464). The net effect of these endothelium-mediated compensatory responses is the maintenance of mean shear stress of the arterial system at ~15–20 dyn/cm^2 (208, 214, 360).

By connecting the external jugular vein to the common carotid artery in mice, Kwei et al. (315) and Abeles et al. (1) have demonstrated that the increases in shear stress and pressure in the vein following its exposure to arterial flow results in its arterialization within weeks, with adaptive responses of the vein wall, including structural and functional reorganization and changes in gene expression profiles. Expression of endothelial adhesion molecules E-selectin and vascular adhesion molecule-1 (VCAM-1) is observed at early time points, concomitant with the presence of neutrophils and monocytes/macrophages in the vascular wall. In addition, endothelium-dependent permeability is decreased in the arterialized vein compared with the contralateral control vein (315). When human saphenous vein segments are perfused ex vivo under arterial versus venous conditions, a significant increase in the production of metalloproteinases (MMPs) with cell proliferation under arterial flow is observed (196, 367). In vein bypass grafting, vascular SMCs migrate and proliferate in the intima, and the vessel wall changes in response to the new arterial environment and its associated shear stress, oxygen tension, metabolite concentrations, and pH (1, 123). Thus exposure to the new biomechanical environment of the arterial circulation is thought to be an important stimulus for the vascular remodeling of a venous bypass graft (73, 315).

In the venous system, changes in hemodynamic forces in the vein wall, including shear stress and pressure, may induce inflammation and the subsequent remodeling of the wall and venous valves, which are the fundamental mechanisms underlying various venous pathologies, including telangiectasias, reticular veins, and varicose veins (424, 446, 448). Study of surgical specimens and direct observation by angioscopy have revealed that the wall and valves of varicose veins undergo profound morphological changes, with thickening in some segments of the wall and thinning in others, dilation of the valve annulus, bulging and stretching of the valvular leaflets, and even complete destruction of the valves (448). These remodeling processes of the vein wall and venous valves involve the complex interplay of a range of factors, including an altered ratio between MMPs and their tissue inhibitors (TIMPs), and elevated levels of cytokines and growth factors that favor an alteration of the extracellular matrix (ECM) (424). In rodent models of venous thrombosis created by ligation of inferior vena cava to produce venous hypertension and altered shear stress (35), thrombus initiation is associated with a rapid vein wall inflammatory reaction

involving early endothelial activation and neutrophil infiltration (35, 157), and later vein wall remodeling associated with increased expressions of MMP-9 and MMP-2 (35, 141). These results on the venous system, in concert with the observations on the arterial system, suggest that changes in hemodynamic forces play critical roles in the remodeling of blood vessels, including both arteries and veins.

B. Endothelial Dysfunction Is a Critical Pathophysiological Factor in Vascular Diseases

The involvement of vascular endothelium in disease processes such as atherosclerosis and thrombosis has been recognized since the time of Virchow (591), but the mechanistic insight into the pathobiology of this process has been developed only recently. It is now appreciated that the normal function of the single-cell-thick endothelial lining of the circulatory system is essential for vascular homeostasis in health and that its dysfunction plays a significant role in many vascular diseases. Clinical evaluation of endothelial function in humans has focused primarily on endothelium-dependent changes in vascular SMC contractility, which is mediated by the release of vasodilators [i.e., endothelium-derived relaxing factors such as NO and prostacyclin (PGI_2)] and vasoconstrictors [i.e., endothelium-derived contracting factors such as thromboxane A_2, free radicals/ROS, endothelin (ET), and angiotensin II] (159, 174, 175, 236). Endothelial dysfunction is often associated with a paradoxical vasoconstriction in response to vasodilating agents such as acetylcholine, due to an impaired activity of endothelial NO synthase (eNOS) or the inactivation of NO by free radicals/ROS such as superoxide anion (236). Paradoxical vasoconstriction with acetylcholine occurs because acetylcholine interacting with its receptors on SMCs leads to vasoconstriction unless inhibited by the acetylcholine-NO axis (159, 352). Several studies have demonstrated that the early stages of atherosclerosis are characterized by a decreased NO bioavailability as a possible consequence of inactivation by superoxide anion (17, 384, 605). In addition to impairments of endothelium-dependent vasodilation, other pathophysiological consequences of endothelial dysfunction specific to atherosclerosis include the following (43, 213, 330):

1. Abnormal vascular reactivity and vasospasm that may cause ischemia, angina, and myocardial infarction;
2. Increased permeability to macromolecules such as lipoproteins;
3. Increased expression of chemotactic molecules (e.g., MCP-1) and adhesion molecules [e.g., intercellular adhesion molecule-1 (ICAM-1), VCAM-1, and E-selectin/P-selectin];
4. Enhanced recruitment and accumulation of monocytes/macrophages in the intima as foam cells;
5. Altered regulation in growth and survival of vascular cells, e.g., decreased EC regeneration and increased SMC proliferation and migration;
6. Disturbed hemostatic balance of thrombotic and fibrinolytic states, e.g., increased expression of procoagulatory molecules such as von Willebrand factor (vWF) and tissue factor (TF), enhanced thrombin generation, platelet aggregation and adhesion, and fibrin deposition.

The pathophysiological factors leading to endothelial dysfunction that are especially relevant to the development of vascular disease include the following (2, 43, 213, 330, 338, 492, 493):

1. Activation by cytokines;
2. Stimulation by free radicals/ROS or oxidative stresses and the advanced glycation end products generated in diabetes and aging;

3. Chronic smoking and hypertension;
4. Chronic exposure to hyperhomocysteinemia and/or hypercholesterolemia;
5. Increased plasma levels of oxidized low-density lipoprotein (LDL) and its accumulation within the vessel wall, as well as infection by bacteria, viruses, and other pathogens with the release of their products (251, 435, 528, 618).

There is increasing evidence that various hemodynamic forces, including fluid shear stress, can also influence the structure and function of ECs and modulate their expressions of pathophysiologically relevant genes (74, 87, 93, 125, 131, 153, 203, 211, 213, 230, 240, 279, 282, 337, 571, 625). The pulsatile flow in the straight part of the arterial tree is laminar with high shear stresses (10–70 dyn/cm^2) (208, 214, 360). Vascular ECs subjected to laminar flow with high shear stress constantly release NO (56, 431, 582). The vascular geometries at arterial branch points, curvatures, and post-stenotic regions lead to disturbances in flow pattern, with a low net forward flow and shear stress (<4 dyn/cm^2), such complex flow patterns without a clear direction play significant roles in inducing endothelial dysfunction, with impairment of NO production (93, 103, 213, 360, 545, 571). At sites of lesion predilection, disturbed blood flow coupled with hyperlipidemia results in EC activation, which leads to fatty streak formation (541). In humans, endothelium-dependent vasodilation is impaired at the branches of coronary arteries (103, 373). An increase in the backward component of pulsatile flow by inflating an occluding cuff around one forearm of healthy men (24 ± 3 yr) to 25, 50, or 75 mmHg for 30 min induces a dose-dependent attenuation of flow-mediated vasodilation in the brachial artery of this arm (565). In the noncuffed arm, no changes in shear rate or flow-mediated dilation are observed (565). In the aorta of hypercholesterolemic LDL receptor-deficient (LDLR$^{-/-}$) mice, the down-regulation of eNOS expression and the upregulation of proatherogenic transcription factors (i.e., Elk-1 and p-CREB) (103, 140) are particularly pronounced at the lesion-prone sites with disturbed flow. An ex vivo study using porcine left common carotid segments has shown that low and reciprocating shear stress (0.3 ± 3 dyn/cm^2) decreases the expression of eNOS gene and NO-mediated vasodilation in response to bradykinin, compared with the unidirectional laminar shear stress (6 ± 3 dyn/cm^2), suggesting that plaque-prone hemodynamic flow patterns impair endothelial function in carotid arteries (199). The endothelial dysfunction (with reductions of eNOS expression and NO production) induced by decreases in blood flow and shear stress can be reversed by physical training to increase the level of shear stress (160, 237, 238). The current state of research on the effects of hemodynamic forces on endothelial biology and pathobiology indicates that elucidation of the role of disturbed flow pattern in endothelial function and dysfunction can provide insights into the mechanisms that predispose specific regions in the vascular system to pathophysiological processes and may help to develop hemodynamic-based strategies for the prevention and management of vascular diseases resulting from atherosclerosis and thrombosis.

III. OCCURRENCE OF DISTURBED FLOW IN PATHOPHYSIOLOGICAL CONDITIONS

Disturbed flow occurs in the vascular system in a number of conditions, including *1*) flow disturbance that naturally occurs in certain regions such as branch points and curvatures of large arteries and the aortic and venous valve sinuses; *2*) flow disturbance generated in arteries through surgical interventions such as end-to-side anastomosis in bypass graft and stent insertion following balloon angioplasty; *3*) flow disturbance in the venous system due to reflux through incompetent valves or outflow obstruction; and *4*) temporal changes in local levels of flow due to sudden cessation and reperfusion in clinical procedures such as organ transplantation. These disturbed flow conditions contribute to the pathogenesis of

many clinical disorders, including atherosclerosis, arterial aneurysm, aortic valve calcification, postsurgical intimal hyperplasia, in-stent restenosis, venous varicosity, chronic venous insufficiency, ischemia/reperfusion injury, and transplant vasculopathy.

A. Correlation of Locations of Atherosclerotic Lesions With Regions of Disturbed Flow in the Arterial Tree

The correlation between the locations of atherosclerotic lesion and the regions of disturbed flow is well documented throughout the arterial system (16, 68, 207, 215–217, 298, 311, 393, 454, 455, 494, 502, 534, 535, 552, 563, 590, 595, 644). These include carotid bifurcations (65, 217, 311, 644, 645), aortic arch (68, 215, 292, 563, 571) (Fig. 4) and branch points of coronary (16, 188, 207, 215, 391, 494, 544), infrarenal, and femoral arteries (393, 454, 455, 534, 535, 563, 595, 613) (Table 1). The nonrandom distribution of atherosclerotic lesions holds true not only for various experimentally induced atherosclerosis (dietary and/or genetic models) and across multiple animal species (monkeys, rabbits, pigs, and rodents), but also for the natural history of this pathological process in humans (31, 55, 68, 105, 106, 109, 205, 215, 406, 502, 547, 563, 590, 623, 644, 651). This site selectivity of atherosclerotic lesions is attributable, at least in part, to the modification of local phenotype and function of vascular ECs by the disturbed flow pattern (viz. flow separation, recirculation, reattachment), low and reciprocating shear stress, and high spatial and temporal gradients of shear stress (263) (Fig. 5). The local differences in flow patterns (laminar vs. disturbed) and in shear stress magnitude or gradient may explain the different rates of atherosclerosis progression among different vessels within the same individual (and even different segments within the same vessel), despite their exposure to the same systemic risk factors such as lipoprotein concentrations (207, 622). Advanced lesions in arteries may cause the weakening of the artery wall, leading to pressure-induced aneurysm and potential rupture, which is also mediated by the complex flow conditions within the aneurysm (476, 498, 514).

B. Contribution of Complex Flow Environments to the Focal Nature of Calcific Lesions in the Aortic Valve

Disturbed flow may occur in the aortic valve sinus and serve as a major contributing factor for valvular heart disease (129, 636). In vitro or ex vivo modeling of aortic valve dynamics suggests that the two sides of the aortic valvular leaflets are exposed to different types of shear stress during systole: low and reciprocating shear stress without a clear direction on the aortic side and unidirectional pulsatile shear stress on the ventricular side (58, 122, 425, 495). This side specificity is in concert with the correlation found between the preferential locations of calcific lesions on the aortic side of the valve and the local hemodynamics experienced by the valvular leaflets (60). In humans (432, 441) and pigs (529), lipid deposits and calcific lesions in the aortic valve occur preferentially in the fibrosa (the layer of the valve immediately beneath the endothelium) on the aortic side of the valve, where complex flow patterns are likely to occur. The preferential susceptibility to lesion formation on the aortic rather than ventricular side of the aortic valve may result from differential regulation of EC gene expression on the two sides, leading to side-specific endothelial phenotypes that favor or inhibit calcification, respectively (129). Thus there is a spatial correlation between the focal nature of calcific lesions and the local hemodynamic environment, similar to that observed for focal atherosusceptibility in the arterial tree (58, 129).

C. Flow Disturbance Associated With Vascular Surgical Interventions

Several types of surgical interventions have been developed with the aim of restoring blood flow in vascular occlusive diseases. These interventions, however, may themselves induce regions of disturbed flow or low shear conditions, thus leading to neointimal hyperplasia and atherosclerotic lesions with poor blood flow that negatively influence the long-term efficacy

of the treatments (472, 568). These clinical conditions include restenosis following angioplasty, in-stent restenosis, and bypass graft failure.

Balloon angioplasty is one of the most common modalities of treatment of coronary artery narrowing and occlusion, but a significant percentage of patients undergoing percutaneous balloon angioplasty would develop restenosis, with vessel wall thickening recurring within the first 6 mo in 30–40% of these cases (289, 394, 420). The frequency of restenosis after angioplasty has been correlated with impaired blood flow with low shear stress, which augments the inward vessel remodeling, cell migration, and activity of genes regulating migration, and significantly exacerbates the reduction in luminal size observed several months after the procedure (511, 604).

The use of stents in angioplasty has dramatically increased since their approval by the United States Food and Drug Administration in 1994, and there have been significant and technological advances. However, restenosis affects 20–40% of de novo coronary lesions treated with traditional bare metal stents (164, 167, 287, 288, 569). This in-stent restenosis is believed to be influenced by abnormal wall stress and disturbed blood flow around the stent (162, 298, 499). Intravascular ultrasound has shown that stent placement in diseased arteries results in a “step-up” phenomenon at the proximal edge of the stent, with the existence of regions with retrograde velocities and flow separation (568). These regions are prone to neointimal hyperplasia and hence in-stent restenosis, suggesting the role of disturbed flow with low and reciprocating shear stress in the development of in-stent restenosis. A randomized, double-blind trial comparing a sirolimus-eluting stent with a bare metal stent in 1,058 patients at 53 centers in the United States who had a newly diagnosed lesion in a native coronary artery has demonstrated that the rate of failure of the target vessel (a composite of death from cardiac causes, myocardial infraction, and repeated percutaneous or surgical revascularization of the target vessel) within 270 days was reduced from 21% with a bare metal stent to 8.6% with a sirolimus-eluting stent (394). Although the drug-eluting stent has led to a reduction in restenosis rate, the optimal approach to treat obstructive atherosclerotic lesions in arterial bifurcations remains unresolved, probably due to the complex patterns of flow and plaque distribution and vessel geometry in these regions (489). It has been estimated that coronary bifurcation lesions are involved in up to 10% of all percutaneous coronary interventions (33). Recent studies on autopsy series have shown a greater prevalence of late stent thrombosis in bifurcation lesions treated with a drug-eluting stent compared with a bare metal stent (176, 409). This late stent thrombosis induced by drug-eluting stent is accompanied by an impaired arterial healing at the flow divider, where the flow disturbance is increased after stent placement, compared with the lateral wall sites (409). Thus the long-term outcomes of the use of drug-eluting stents in bifurcation lesions may be tempered by an increased risk for thrombosis by stent-induced flow disturbances, which may influence drug deposition, arterial healing poststenting, and local fibrin and platelet deposition (21, 177, 267, 304, 408, 409).

Neointima hyperplasia is a major cause of late graft failure in arterial bypass grafting using either artificial vascular graft or a vessel segment from the patient, usually the saphenous vein (102). The insertion of a segment of the saphenous vein into the arterial system exposes the thin-walled and compliant vein to the pressure and shear stress in the arterial system that are much higher than what the venous wall is prepared to accommodate. This mechanical mismatch may cause the saphenous vein segment to bulge, thus resulting in a geometric mismatch that would lead to disturbed flow and vulnerability to neointimal hyperplasia and atherosclerosis downstream of the anastomosis, with the subsequent failure of bypass grafts (86, 295, 348). In addition, the saphenous vein is generally larger in diameter than the grafted coronary artery, resulting in reduced linear velocity of flow in grafting (194, 531). Any existing bicuspid valves in the saphenous vein graft may cause further impediment and

become sites of flow disturbance, especially when two valves are present in the body of a single saphenous vein graft (530). Thrombus formation at or distal to these valves results in early graft occlusion after bypass surgery (382, 530, 533). Surgical modifications using vein cuffs to shape the curvatures of distal anastomosis of arterial bypass grafts can alter the location of low shear stress, with a corresponding shift in the area of neointimal hyperplasia (297), indicating that disturbed flow with low shear stress plays important roles in mediating the process of neointimal hyperplasia. Using the photochromic tracer technique to visualize the variations of shear stress in a 30° anastomosis in the absence (disease-free model) or presence of intimal hyperplasia (disease model produced by fitting the wall of the native artery with an elliptical plug to simulate the presence of intimal hyperplasia on the bed), Ojha (434) showed the occurrence of reduced gradients of shear stress downstream to the anastomosis in the diseased model compared with the disease-free model, suggesting that the development of anastomotic intimal hyperplasia may initially be a compensatory response resulting in a reduction of disturbed flow region.

D. Disturbed Flow Pattern Around Venous Valves and Its Pathophysiological Role For Thrombosis Initiation

Veins bring partially deoxygenated blood from the organs and tissues to the right heart and lungs, where it is reoxygenated. The venous system of the lower limbs consists of an interconnected network of superficial veins (e.g., great and lesser saphenous veins), perforator veins, and deep veins (e.g., femoral and popliteal veins) (478). A series of bicuspid valves is located throughout the superficial and deep veins to ensure blood flow movement in the cephalad direction, preventing the reflux of blood toward the feet while in the upright posture (163, 396). Perforating veins also contain one-way valves that prevent reflux of blood from the deep veins into the superficial system. Early studies on the flow behaviors of model particles and red blood cells through an isolated transparent dog saphenous vein containing a two-leaflet valve show a large primary recirculation eddy as well as a small secondary eddy in each valve pocket (285, 286). Developments in ultrasound technology supplemented by B-mode and pulsed-wave Doppler scanning have allowed detailed noninvasive in situ visualization of the valve with its cusps and the flow of blood through the valve (354). In normal physiological conditions, venous flow is pulsatile and venous valves open and close ~20 times/min while a person is standing (8, 36, 354). The movements of the valve cusps undergo four phases that constitute the valve cycle. In the opening phase, the cusps move from the closed position toward the sinus wall. In the equilibrium phase, the valves cease opening and the leading edges remain suspended in the flowing stream and undergo self-excited oscillations that resemble flutter of flags in wind. In the closing phase, the leaflets move synchronously toward the center of the vein. In the closed phase, the cusps remain closed (354). During the equilibrium phase, flow through the valve separates into a proximally directed jet in the center of vein and a recirculation eddy into the sinus pocket behind the valve cusp with reattachment at the wall of the sinus (Fig. 6). The central jet possibly facilitates outflow, and the recirculation eddy prevents stasis in the pocket to ensure all surfaces of the valve being exposed to shear stress. Valve closure occurs when the pressure caused by the recirculation eddy exceeds the pressure on the luminal side of the valvular leaflets as a result of the proximally directed jet. Thus venous valves are operated by pressure rather than driven by flow so that little or no reflux occurs in bringing about complete closure of the valve (36, 475).

There are several features of the venous valves that render these regions highly vulnerable to the initiation and formation of thrombosis (8). First, ECs lining the valve pocket are exposed to disturbed flow with reduced shear stress or even stasis due to immobilization during all phases of the valve cycle (354). This reduced flow or stasis in the valve sinus is shown by the finding that contrast media linger in valve sinuses for an average of 27 min post-

venography (372). This valve sinus stasis may modulate the expression of thrombotic factors in these ECs and prevent the efflux of activated clotting factors and influx of clotting factor inhibitors, constituting a potentially hypercoagulable microenvironment (52). Second, the blood in the cusps of the valve is relatively hypoxic (235), which has been well documented to induce inflammatory responses of ECs, with increased generation of intracellular ROS that plays important roles in vascular pathologies (238, 366). Third, there is a tendency for white blood cells (WBCs) and platelets to become trapped in the valve pocket due to flow recirculation or stasis. For example, Ono et al. (436) have shown infiltration of valvular leaflets and the venous wall by WBCs (monocytes and macrophages) in all valve specimens from patients with chronic venous diseases, but in none from controls. Further work by Takase and co-workers (559, 561) has confirmed this phenomenon. This is in keeping with Virchow's triad (49, 262, 276, 316, 359, 606), which indicates that local thrombosis may occur when the flow velocity or pulsatility is reduced, the hemostatic balance is altered, and/or the vascular integrity is lost (8). Indeed, direct evidence from autopsy studies and phlebography, as well as circumstantial evidence such as the correlation between the frequency of deep venous thrombosis and the number of valves in individuals, have revealed that the sinus of venous valves is a frequent location of thrombosis initiation (52, 452, 512). The thrombus begins as a microscopic nidus of fibrinred cell collections near the apex of the valve pocket (8). Regions of endothelium adjacent to venous valves are common sites of WBC and platelet accumulation and EC injury (169). Thus the sinus of venous valve is a unique microenvironment in some respects similar to the microenvironments present in other specific vascular niches prone to atherosclerosis and thrombosis.

E. Flow Disturbance Due to Blood Reflux Through the Incompetent Valves and Outflow Obstruction in the Venous System

Incompetence of venous valves, which may occur as a result of pathological dilatation, inflammation, or deterioration of the vein wall, clot-related scarring, or an inherited valve abnormality, allows venous reflux or retrograde flow, which leads to altered pressure and shear stress that underlie the clinical manifestations of chronic venous diseases, including varicose veins and chronic venous insufficiency (36, 222, 376, 478). A small degree of reflux may occur in the presence of a normally functioning valve (500). The duration of reflux (or the reflux time) of >0.5 (or 1.0) second is used to diagnose the presence of abnormal reflux, although a more refined definition with a variable "cutoff" value based on the location of the vein has been suggested (163, 318). A longer reflux time implies more severe disease. Other parameters such as the peak reflux velocity (>10 cm/s) and the calculated reflux volume have also been used to assess the severity of reflux (163, 319, 376, 412, 423).

The obstruction of the deep veins, which limits the return of blood from the limbs to the heart and results in venous hypertension (30, 415, 477), is also a major cause leading to chronic venous insufficiency and increasing the risk for pulmonary embolism. The most common cause of obstruction is deep vein thrombosis; other causes are inherited abnormalities, inadequate recanalization or venous stenosis, and compression of the vein, e.g., from a tumor or bandage (30). These clinical conditions may further damage and destroy venous valves, leading to the worsening of venous reflux. In patients with severe clinical diseases, combination of reflux and obstruction is seen more frequently than reflux or obstruction alone (415).

Mellor et al. (376) have demonstrated that mutations in the Foxc2 gene, which is located on chromosome 16 (421) and is expressed in both ECs and SMCs of developing blood vessels (313) and on the venous and lymphatic valvular leaflets (457, 621), are strongly associated with primary valve failure in veins of the lower limb and result in lymphedema distichiasis, an inherited primary lymphedema in which a significant number of patients have varicose

veins (376). Investigations by color Duplex ultrasound in 18 participants with a Foxc2 mutation reveal reflux in the great saphenous vein that every one of the 18 (compared with only 1 of 12 referents that include 10 family members), and that 14 of these 18 participants also have deep vein reflux (376). The extent of disturbance in venous flow by reflux depends on the magnitude of ret- rograde flow, which is generally greater in refluxing superficial veins than in refluxing deep veins (376). The walls and valves of the superficial veins are more prone to structural failure than the deep veins, probably because the deep veins are better supported by muscle and fascia, whereas superficial veins are only surrounded by loose connective tissue and fat (163, 376). This is in keeping with the finding that superficial veins fail before deep veins during the progression of venous disease (317, 376, 390). Chronic venous reflux is associated with increases in interactions between WBCs and ECs (34) and the numbers of activated WBCs (436), which can lead to the activation of ECs and upregulation of proinflammatory genes that underlie the clinical manifestations of chronic venous diseases (34).

F. Flow Disturbance Due to Stagnation and Reperfusion

An additional form of flow disturbance that mediates endothelial dysfunction is the cessation or stagnation of flow and its later recovery in clinical conditions associated with ischemia/reperfusion or hypoxia/reoxygenation injury, which complicates myocardial recovery following acute infarction, and can result in cell damage, arrhythmia, and death (182, 503, 612). Endothelial dysfunction is also associated with tissue injuries induced by trauma resuscitation, solid organ transplantation, and major vascular surgical interventions, which result in inflammatory responses with recruitment of WBCs (such as neutrophils) from the microcirculation (4, 460, 496). Hypoxia and reoxygenation have been well documented to induce EC inflammation and EC-WBC interactions, which play important roles in the pathogenesis of vascular diseases (305, 366). For more information about vascular/endothelial responses to ischemia/reperfusion or hypoxia/reoxygenation injury, the reader is referred to several excellent reviews (4, 66, 223, 299, 325, 597).

IV. EFFECTS OF DISTURBED FLOW ON VASCULAR ENDOTHELIUM IN VITRO

A. In Vitro Models For Studying the Effects of Disturbed Flow on ECs

In the past decades a variety of in vitro systems for applying shear flow to ECs have been developed in an attempt to reproduce important features of in vivo flow environments of ECs to gain insight into the mechanisms of their responses to shear stress. These systems include those based on the principles of parallel-plate flow chamber (185, 198, 245, 308, 326, 333), cone-and-plate viscometer (40, 132, 149, 150, 249, 504), parallel disk viscometer (324), orbital shaker (453, 640), and rectangular or tubular capillary tube (392, 456, 482) (Fig. 7). The systems using parallel disk viscometer and orbital shaker do not result in a uniform shear stress across the entire monolayer, and the capillary tubes do not yield sufficient amounts of cells for some bioassay analysis. Systems based on the principles of parallel-plate flow chamber and cone-and-plate viscometer have been widely used for studying EC responses to shear stress in terms of molecular signaling and gene expression, because of their capability of producing a wide range of magnitudes of uniform shear stress on ECs and thus allowing the collection of sufficient amount of cells for analysis. The parallel-plate flow channel is created by using a gasket with a rectangular cutout to result in a uniform channel height along the path of flow, which is commonly generated between two slit (manifold) openings at either end of the rectangular chamber by a constant pressure head, syringe pump, or peristaltic pump (Fig. 7*A*). This parallel-plate approach holds many practical attractions, including homogeneity of the force stimulus, simplicity of the equipment, ease of medium sampling/exchange, and ease of access to the culture (both

physically and for microscope visualization) (53). The flow in the cone-and-plate system is generated by rotation imposed around a cone axis oriented perpendicular to the surface of a flat plate (Fig. 7*B*). Since both the local relative velocity and the separation between the cone and plate surfaces vary linearly with the radial position, this configuration achieves spatially homogeneous shear stress on both surfaces, as well as the fluid in the gap (53). Depending on the cone taper and the imposed angular velocity, a wide range of shear stresses can be achieved, extending even into the turbulent flow regime (53, 132). Direct microscopic visualization is also feasible (504), albeit somewhat cumbersome, with the advantage of small volumetric fluid requirement (53). All these devices allow the determination of the effects of uniform laminar shear stress on cultured endothelial cells. To study the effect of spatial variation of laminar shear stress on ECs, Usami et al. (584) designed a parallel-plate flow chamber in which a tapered channel is used to create a linear variation of shear stress, starting from a predetermined maximum value at the entrance and falling to zero at the exit, enabling the study of EC responses to a wide range of shear stress using a single run at constant flow.

Several in vitro models capable of producing disturbed flow have been established on the basis of parallel-plate flow chamber and cone-and-plate viscometer to simulate some of the features of complex flow patterns in the vascular tree. In the cone-and-plate viscometer, this can be achieved by imposing a rectangular obstacle. In the parallel-plate flow chamber, a step near the inlet can be created by using two silicone gaskets with the top one having a longer longitudinal cutout than the one below (Fig. 8), resulting in a backward-facing step (i.e., vertical-step) flow in the channel (28, 76, 88, 94, 134, 147, 148, 259, 349, 379, 405, 458, 532, 564, 576). The step-flow channel is characterized by a well-defined recirculation eddy immediately downstream of the step, followed by a region of flow reattachment and finally a unidirectional laminar flow that is reestablished further downstream (Fig. 9) (88, 94). When ECs are subjected to shear flow in a step-flow channel, their responses to both laminar and disturbed flows can be studied in the same monolayer (for summary, see Table 2). However, it is difficult to use standard immunoblotting techniques to analyze the effects of disturbed flow on EC signaling and gene expression in the step flow channel, because the local hemodynamic environments in the channel vary with a length scale of only tens to hundreds of micrometers with only a few cells being exposed to the flow disturbances (approximately hundreds of cells in a 1-mm span of the confluent monolayer) (134). Therefore, alternative experiments have been performed to study the effects of reciprocating flow in a parallel-plate flow chamber (with the use of a reciprocating flow pump) (87, 259), a cone-and-plate viscometer (266, 536, 537), or an orbital model (119). The aim of these reciprocating flow devices is to create a reciprocating flow without a significant forward direction, which is a main feature of the disturbed flow, that allows the acquisition of sufficient amount of cells for analysis by a variety of bioassays. These devices, however, do not allow the study of the responses of ECs to different shear flow patterns in the same chamber.

In an attempt to better approximate the actual wall shear stress experienced by ECs in arterial systems in vivo and to understand how these stimuli affect endothelial responses, Blackman et al. (41) have developed a cone-and-plate dynamic flow system that can produce pulsatile shear stresses in an arterial-like waveform that mimics the flow characteristics in human arteries, e.g., a previously defined waveform of the human abdominal aorta of a healthy volunteer that has been characterized by both magnetic resonance and ultrasound imaging techniques (41, 358). A series of research studies have been conducted using this sophisticated in vitro dynamic flow system with the impositions of actual shear stress waveforms from carotid bifurcations or coronary collateral vessels (115, 116, 355, 444), which represents a significant advance over the earlier studies on the responses of ECs to disturbed flow using a relatively simplified shear flow system. This

dynamic flow system is also used to investigate the differential role of arterial and venous shear stress waveforms (derived from human abdominal aorta and saphenous vein, respectively) in modulating the responses of arterial and venous ECs to cytokine tumor necrosis factor-α (TNF-α) (347). Research using these common in vitro shear flow systems has helped the investigation on EC functions in both physiological and patho-physiological conditions.

B. Effects of Disturbed Flow on EC Morphology, Cytoskeletal Organization, Proliferation, and Migration

ECs exposed to disturbed flow with a low and reciprocating shear stress (e.g., with a mean value of only ~0.5 dyn/cm^2 and a pulsatile oscillation of ±4 dyn/cm^2) and laminar flow with a relatively high shear stress (10 –20 dyn/cm^2) show differential responses, in terms of molecular signaling, gene expression, structure, and function. For example, ECs exposed to disturbed flow in a step-flow channel (i.e., areas *a* and *c*, with mean shear stress values of 0.5 and 0 dyn/cm^2, respectively) are round in shape (Fig. 10), with random and short actin filaments located mainly at the periphery of the cells (Fig. 11) (94). In contrast, ECs exposed to laminar flow (i.e., areas *b* and *d*, with opposite flow directions) with a relatively high shear stress (20 dyn/cm^2) are aligned in the direction of flow, with the formation of very long, well-organized, parallel actin stress fibers in the central region (Figs. 10 and 11) (94, 147, 149, 172, 187, 243, 294, 333, 483). These results on EC morphological changes are comparable with in vivo observations in the primate thoracic aorta (107, 125, 128, 134) that ECs are elongated and aligned with the longitudinal axis of the vessel in the straight, nonbranch areas and that they have a polygonal morphology in regions around branches, where the shear stress oscillates back and forth over the cardiac cycle (Fig. 12). In vivo studies have also shown that low shear stress favors prominent peripheral actin microfilaments (294, 592), while high shear stress promotes an increase in central actin stress fibers (294, 322).

ECs exposed to disturbed flow in a step-flow channel turn over more rapidly than those kept in static conditions (86, 94, 148, 337, 564), with their DNA synthesis rate being significantly higher in the reattachment area than in the laminar flow area or under static condition (86, 87, 94) (Fig. 13). This enhancement of EC proliferation by disturbed flow is accompanied by a sustained activation of extracellular signal-regulated kinase (ERK) (337) and is suggested to be regulated by the inhibition of the p21^{CIP1}-suppression of cyclin-dependent kinase activity to allow G_0/G_1-S transition (9, 126). Turbulent fluid shear stress also induces vascular EC turnover in vitro (132). In contrast, a high level of laminar shear stress inhibits DNA synthesis (9, 94) and proliferation of ECs (334), with a reduction of the number of cells entering the cell cycle and arrest of the majority of cells in the G_0/G_1 phase (9, 342, 648). These in vitro results are comparable with the in vivo findings that ECs at the branch points of human iliac arteries (where disturbed flow predominates) have shorter telomeres and a focal acceleration of senescence (70, 103). Early studies on in vivo uptake of tritiated thymidine with subsequent autoradiography of Haütchen (en face) preparations of guinea pig aortic endothelium show that mitosis is most frequent in the aortic arch and around the orifices of branches, where the local flow is disturbed (626). Later studies on light microscopic examination of the luminal surface of the entire rabbit thoracic aorta also reveals that ECs in regions of disturbed flow exhibit higher mitotic rates (86, 97). Guo et al. (228) have shown that distinct modes of interactions between AMP-activated protein kinase (AMPK) and Akt play important roles in the regulation of EC cell cycle by laminar versus disturbed flows. Laminar shear stress activates both AMPK and Akt in ECs; the counterbalance between the antimitotic AMPK and the proliferative Akt results in relatively undisturbed mTOR (mammalian target of rapamycin) and its target p70 ribosomal S6 kinase (p70S6K). Thus EC entrance into the mitotic S and G_2/M phases is attenuated, and

endothelial homeostasis is maintained. In contrast, disturbed flow activates only Akt; the lack of AMPK activation to generate an antagonistic effect leads to a sustained activation of p70S6K and, consequently, a high proportion of ECs in the mitotic state.

Laminar shear stress significantly enhances EC migration in wound healing in the flow channel in vitro (11, 13, 259) and canine carotid-femoral grafts in vivo (628), whereas disturbed flow has no significant promoting effect on wound healing (Fig. 14). There is evidence that disturbed flow causes cell loss and the migration of ECs away from areas with a high shear stress gradient (564). The shear-induced directional migration is related to the shear-mediated lamellipodia protrusion and focal adhesions remodeling, which are regulated by Rho family small GTPases (133, 260, 336, 337).

C. Effects of Disturbed Flow on EC Permeability and Junctional Proteins

The intact intercellular junctions of the normal endothelium in the straight part of the arterial tree do not allow the passage of macromolecules such as lipoproteins, except during EC turnover (86, 345, 607). The atheroprone areas such as the branch points, where blood flow is disturbed, have an increase in permeability to macromolecules, including ^{131}I-albumin (32) and Evans blue dyelabeled albumin in the pig (250) and rabbit (86, 97) aorta, and low-density lipoprotein (LDL) or fluorescent, radiolabeled and chromogenic tracer particles in normal or cholesterol-fed rabbit aorta (506, 507, 540, 542, 611). Many of these in vivo observations have been reproduced in in vitro studies. A step-flow channel has been used to show that the transendothelial transport of dextran (mol wt 70,000) in the vicinity of flow reattachment is significantly higher than that in the laminar flow area (458). ECs in regions of disturbed flow in the rabbit thoracic aorta in vivo (128) and the step-flow channel in vitro (94, 148) also have higher mitotic or turnover rates compared with ECs in other regions, where flow is unidirectional, providing evidence in support of the “cell turnover-leaky junction hypothesis” (79, 97, 261, 344, 345, 609).

The modulations of the expression and structure of permeability-related intercellular junctional proteins, including connexins (Cx) and vascular endothelial (VE)-cadherin (104, 142, 147, 379) by disturbed flow provide insights into the mechanisms by which disturbed flow enhances endothelial permeability. Disturbed flow causes an upregulation of Cx43 in ECs, but the distribution of Cx43 is discontinuous at the EC periphery, as demonstrated by the in vivo observations at vascular branch points in the rat aorta (195) and in the intima of atherosclerotic lesions in humans and rabbits (466, 467), as well as in vitro experiments using a step flow channel (134, 147). In vivo studies on the rat aorta have shown that compared with the strong staining of VE-cadherin at EC borders in the descending thoracic aorta, where the pulsatile flow has a net forward component, there is only a faint staining in the aortic arch and the poststenotic dilatation site beyond an experimental constriction, where the flow is reciprocating with low net flow (379). In vitro flow channel experiments have shown that shortterm exposure (6 h) of ECs to either reciprocating (0.5 ± 4 dyn/cm^2 at 1 Hz) or pulsatile (12 ± 4 dyn/cm^2 at 1 Hz) flow causes disruption of VE-cadherin and its associated protein β-catenin at cell borders (Fig. 15) (379). However, these junctional VE-cadherin and β-catenin molecules reappear as continuous distributions after sustained exposure (24 h or longer) to pulsatile flow, but not reciprocating flow (Fig. 15). The differential expressions and distributions of gap junction proteins in regions of disturbed flow may contribute to the junction discontinuity and consequently enhanced macromolecular permeability.

D. Effects of Disturbed Flow on EC Signaling and Gene Expression

By using microdissection and antisense RNA amplification methods, Davies et al. (134) demonstrate by DNA microarray studies that ECs isolated from disturbed flow regions

exhibit a greater degree of heterogeneity in gene expression than those from laminar flow regions and that the heterogeneity in disturbed flow regions may contribute to the focal initiation of atherosclerotic lesions (27, 130, 134). ECs subjected to disturbed flow in a step-flow channel exhibit localized increases in the levels of transcription factors such as nuclear factor-κB (NF-κB), early growth factor-1 (Egr-1), c-*fos*, and c-Jun in their nuclei (405) and enhanced expressions of ICAM-1 and E-selectin, but not VCAM-1, on their surfaces (88). ECs in the disturbed flow region of a step-flow channel also exhibit a sustained activation of sterol regulatory element (SRE) binding protein (SREBP), which acts to increase the SRE-mediated transcriptional activation of EC genes encoding for LDL receptor, cholesterol synthase, and fatty acid synthase, with the consequent enhancement of LDL uptake and lipid synthesis (349), compared with ECs exposed to laminar flow at high shear stress or maintained under static condition. Compared with human coronary arterial ECs exposed to laminar flow, those exposed to disturbed flow express higher levels of toll-like receptor-2 (TLR-2) (161), whose deletion in hyper-lipidemic $LDLR^{-/-}$ mice is atheroprotective (400). The responsiveness of ECs to agonists of TLR-2 such as lipopolysaccharide and TNF-α, which are augmented in activated ECs of atherosclerotic lesions (166), is blocked by laminar flow, but not by disturbed flow, in a step-flow channel (161).

ECs exposed to low and/or reciprocating shear stress created in a parallel-plate or cone-and-plate chamber show sustained expressions or activations of NF-κB (387, 388, 537); Sp1 (640); Egr-1 (119, 640); ICAM-1 (72, 119, 537, 640); VCAM-1 (72, 388); E-selectin (72, 119, 640); MCP-1 (257, 265); MMP-9 (200, 357); TF (368); ET-1 (474, 653); prepro-ET-1 (114); calcium/calmodulin-dependent protein kinase II (CaMKII) (64); bone morphogenic protein (BMP)-4 (536, 537) and its antagonists follistatin, noggin, and matrix Gla protein (71); $gp91^{phox}$ [a major component of NAD(P)H oxidase complex] and its member Nox-4 (258, 266); sphingosine kinase-1 (SphK1, an enzyme that catalyzes the conversion of sphingosine to sphingosine-1 phosphate to play inflammatory and proliferative roles) (77); p21-activated kinase (PAK, a Ser/Thr kinase that modulates small GTPases Rac and Cdc42-induced cytoskeletal remodeling) (440); cathepsin K (a lysosomal cysteine ECM protease) (461); Shc (350), c-Jun- NH_2-terminal kinase (JNK) (229); PDGF-DD (a novel mediator of SMC phenotype) (566); and HuR (a stress-sensitivity regulator gene that plays inflammatory roles) (487), as well as elevations of oxidative stress or ROS levels due to continued increases of intracellular superoxide and NADH oxidase activity (138, 139, 258, 374, 526, 536). The upregulation of virtually all of these atherogenic or proinflammatory genes in ECs in response to low or reciprocating flow (with little mean flow rate) are either absent or transient in cells subjected to steady or pulsatile laminar flow with a positive mean flow rate, which may even cause opposite effects (downregulation); these upregulations are also not seen in ECs maintained under static conditions (14, 290, 321). Moreover, steady laminar flow upregulates the expression or activity of cytoprotective genes/proteins including the complement-inhibitory proteins clusterin (583) and CD59 (296), antioxidant enymes superoxide dismutase (SOD) (570), heme oxygenase-1 (HO-1) (78, 254), NAD(P)H quinone oxidoreductase 1 (NQO1) (254), peroxiredoxins (PRX) (395), mitogen-activaed protein kinase (MAPK) phosphatase (MKP-1) (642), eNOS (23, 44, 136, 258, 474, 570) and its essential cofactor tetrahydrobiopterin (615), and angiopoietin-2 (Ang-2) (574), as well as induces productions of PGI_2 (184, 474), NO (56, 431, 582), and intracellular glutathione (GSH) (397), which are considered anti-atherogenic.

Laminar flow induces EC phosphorylation of GTP cyclohydrolase I (GTPCH-1), which is the rate-limiting enzyme involved in de novo biosynthesis of tetrahydrobiopterin and undergos negative-feedback regulation by tetrahydrobiopterin via interaction with GTP cyclohydrolase feedback regulatory protein; this mechanism may be involved in the flow regulation of EC NO production (335). In contrast, reciprocating flow does not cause the inductions of CD59, HO-1, PRX, and eNOS, nor the production of NO and PGI_2 (199, 296,

527, 653), and it decreases intracellular GSH (397) and GTPCH-1 phosphorylation (335). Some of the protective effects of laminar shear stress are mediated through the inhibition of cytokine- induced signaling and gene expression in ECs (38, 89–92, 422, 445, 554, 578, 579, 633, 634) and EC apoptosis (127, 154–156, 202, 249, 459), as well as the modulation in SMC phenotype (577). The HO-1 expression in ECs induced by statin (a 3-hydroxy-3-methylglutaryl-coenzyme A reductase antagonist that exhibits lipid-independent immunomodulatory, anti-inflammatory, and cholesterollowering properties) is enhanced by laminar shear stress, but markedly attenuated by reciprocating flow (12). Disturbed flow increases the activation and splicing of X-box binding protein-1 (XBP-1), a key signal transducer in endoplasmic reticulum stress response; overexpression of spliced XBP-1 induces apoptosis of ECs and endothelial loss from blood vessels during ex vivo cultures because of caspase activation and downregulation of VE-cadherin resulting from transcriptional suppression and matrix metalloproteinase-mediated degradation (647). Conklin et al. (101) demonstrate that low shear stress results in significant increases in EC mRNA and protein expressions of vascular endothelial growth factor (VEGF), an endothelial-specific mitogen that increases vascular permeability and is present in human atherosclerotic lesions, compared with the physiological levels of laminar shear stress. These changes in VEGF expression may suggest a possible molecular mechanism for increased endothelial permeability in regions of disturbed flow with low shear stress in addition to the changes in junction proteins discussed above. Moreover, the increases in calcium influx and chloride current induced in EC monolayer by steady and pulsatile laminar flows are not seen with reciprocating flow (204, 244). Flow-activated ion currents exhibit different sensitivities to shear stress magnitude and oscillation frequency (341).

Studies using genomic approaches have further demonstrated that different flow patterns or shear stress distributions differentially regulate EC gene expression (50, 51, 60, 115, 201). Thus disturbed flow or shear stress applied with an athero-prone waveform replicating those in regions of disturbed flow in vivo leads to the upregulation of several pro-atherogenic genes. In contrast, exposure to laminar flow or shear stress with atheroprotective waveform increases the expression of sets of atheroprotective genes (50, 51, 60, 75, 115, 116, 201, 370, 652). Of great interest is the induction of the atheroprotective transcription factor Krüppel-like factor (KLF)-2 in ECs by atheroprotective flow waveform. KLF-2 is downstream of the MAPK ERK5 (444), which appears to play a central role in the expression of atheroprotective genes and maintenance of atheroprotective quiescent endothelial phenotype (143–145, 346, 444, 509). Young et al. (638) have demonstrated that flow-induced KLF-2 expression is mediated by the activation of AMPK. Other studies have identified nuclear factor erythroid 2-like 2 (Nrf2) as a shear-induced transcription factor responsible for antioxidant gene expression (78, 116, 254). Athero-prone and atheroprotective flow waveforms differentially regulate EC redox state and antioxidant potential through the phosphoinositol 3-kinase/Akt-dependent activation of Nrf2 and its downstream transcriptional targets (116). KLF-2 enhances the nuclear localization of Nrf2, and the combined actions of KLF-2 and Nrf2 constitute ~70% of the shear stress-induced gene expression in ECs (45, 179).

There are several epigenetic mechanisms that may modulate the gene expression and cellular function in response to various forms of shear stress. For example, recent evidence suggests that histone deacetylases (HDACs), which are a class of enzymes that regulate the structure and function of chromatin and some transcription factors and hence gene transcription, are involved in shear pattern-mediated gene expression and function in ECs. Exposure of ECs to laminar shear stress at 24 dyn/cm^2 induces phosphorylation-dependent nuclear export of HDAC5, which is involved in shear inductions of KLF-2 and eNOS (601). On the other hand, exposure of ECs to disturbed flow created by an orbital shaker induces serine/threonine phosphorylation of HDAC3, which serves as a pro-survival molecule with a

critical role in maintaining endothelial integrity (643). Shear stress induction of c-*fos* gene in ECs is mediated by shear-induced acetylation and phosphoacetylation of histone H3 via p38 MAPK- and protein kinase A (PKA)-dependent pathways (270). In addition, the recently discovered microRNAs, which bind to messenger RNAs to interfere with their translational process, play a significant role in the regulation of gene and protein expressions and hence a variety of biological processes (430, 551, 585). Recent studies by Qin et al. (473) and Wang et al. (599) demonstrate that application of laminar shear stress (12 dyn/cm^2) to ECs regulates the EC expression of many microRNAs, including microRNA-19a and -23b, which are involved in flow regulation of EC cell cycle or growth. However, there is a lack of research on microRNAs under disturbed flow, and studies on this important topic are needed.

E. Effects of Disturbed Flow on EC-WBC Interactions

Adhesion of circulating WBCs to and their subsequent transmigration across the EC monolayers are critical events leading to vascular disorders such as inflammation and atherosclerosis (197, 491, 493). In vivo, both the local fluid dynamics of arterial flow (364) and the SMCs located in close proximity to ECs (646) exert significant influences on WBC recruitment into the vessel wall. Since the 1970s, studies by Goldsmith, Karino, and others have contributed to the understanding of fluid dynamic and rheological bases of complex blood flow in arteries resulting from the interplay of blood components and vessel geometry (85, 283, 284). Studies using the step-flow channel have shown that the adhesion of monocytes on ECs occurs preferentially in the vicinity of the reattachment point in disturbed flow (28, 88) (Fig. 16). In contrast, sustained laminar flow with a high shear stress inhibits the cytokine-induced signaling and gene expression and the adhesion of monocytes to activated ECs (88, 633, 634). The preferential distribution of monocyte-EC adhesion in regions of disturbed flow may be attributable to *1*) the altered expression of adhesive proteins such as ICAM-1 and E-selectin on EC surfaces (88) and/or *2*) the enhanced collisions and prolonged contacts between the circulating monocytes and ECs, as a result of a higher near-wall concentration, a longer residence time, a greater normal (perpendicular) velocity component towards the wall, and a smaller tangential velocity component along the wall in these regions (28, 88). By coculturing ECs with SMCs in collagen gels, Chen et al. (76) have demonstrated that the adhesion and transmigration of monocytes, neutrophils, and peripheral blood lymphocytes is increased by disturbed flow, particularly in the reattachment area, and that these cells exhibit different migratory behaviors beneath the EC monolayers (Fig. 17). In addition, neutrophils, peripheral blood lymphocytes, and monocytes all roll more slowly and transmigrate more rapidly in regions near the reattachment point compared with other areas. Coculture of ECs with synthetic-phenotype SMCs induces the EC expressions of various adhesion molecules and chemokines that contribute to the enhancements of WBC adhesion to and transmigration across the cocultured ECs (76). These findings demonstrate the importance of the dynamic flow environment and the underlying SMCs in modulating interactions between the circulating WBCs and the ECs, which may contribute to the regional propensity for WBC recruitment in disturbed flow areas.

F. Effects of Temporal Gradient of Shear Stress on EC Signaling and Gene Expression

In addition to the spatial gradient of shear stress at vessel bifurcations and in the step-flow channel, the temporal gradient of flow also regulates EC functions. In contrast to the inductions of ERK phosphorylation and c-*fos*, PDGF-A, and MCP-1 expressions by increases in flow as a step function (nearly instantaneous increase of shear stress from 0 to 16 dyn/cm^2, followed by steady shear for a sustained period) or an impulsive function (a 3-s impulse of 16 dyn/cm^2) (24, 26), these inductions do not occur with a ramped increase in flow [shear stress smoothly transitioned from 0 to 16 dyn/cm^2 over 2 min (for ERK activity)

or 5–10 min (for gene expression), and then sustained for a desired period]. Such differential modulations of signaling and gene expression in ECs by varying the rate of rise of shear flow are accompanied by (and probably attributible to) the corresponding changes in transcription factors NF-κB and Egr-1 mediated by NO (26). Furthermore, White et al. (614) have shown that the enhanced EC proliferation at the reattachment area in the step-flow channel seen with a step increase in flow does not occur in response to ramp-flow application. The cell proliferation induced by high temporal gradient in shear involves the activation of ERK in ECs (25). Application of laminar flow as a step function to an EC monolayer stained with 9-(dicyanovinyl)-julolidine, which is a fluorescent probe that integrates into the cell membrane and changes its quantum yield with the viscosity of the environment, results in a decrease in fluorescence intensity, indicating an increase of membrane fluidity (233), which in turn leads to the activation of heterotrimetric G proteins (227). By using a fluorescence recovery after photobleaching technique to measure lipid lateral diffusion coefficient of EC plasma membranes labeled with 1,1′-dihexadecyl-3,3,3′, 3′-tetramethylindocarbocyanine perchlorate, Butler et al. (62) demonstrate that the increase in EC membrane fluidity and the consequent ERK and JNK activation induced by the application of laminar shear as a step function do not occur with ramp flow. Thus the plasma membrane lipids are receptive to fluid shear stress (61, 62, 233). Using the isolated vessel ex vivo perfusion system, Butler et al. (63) have shown that the initial potent and transient vasodilation induced by flow is dependent on the ramping rate of the shear flow and that the second phase of modest and sustained vasodilation is dependent on the shear magnitude. All these findings indicate that temporal gradient in shear stress plays important roles in modulating signaling and gene expression in ECs, and consequently their functions.

V. IN VIVO EXPERIMENTAL MODEL STUDIES ON THE EFFECTS OF DISTURBED FLOW ON VASCULAR ENDOTHELIUM

A. In Vivo Experimental Models of High and Low Shear Stresses

In contrast to the many in vitro studies on the effects of disturbed flow on ECs, there have been limited numbers of in vivo investigations on EC responses to disturbed flow, mainly due to the lack of appropriate in vivo models that can generate well-controlled flow patterns and the difficulty of determining the molecular and cellular responses in vivo. Nevertheless, several animal models have been created to study the effects of high and low shear stresses on EC/vascular responses. The commonly used models of high shear stress in studies on rabbits and rats include *1*) the creation of an arteriovenous fistula, often using carotid or femoral arteries (309, 365, 411, 516, 518, 575); *2*) ligation of one of the carotid arteries to induce increases in flow and shear stress in the contralateral carotid artery (252, 300, 306, 365, 378, 624); and *3*) transposition of a vein graft into the arterial circulation, thus increasing the shear stress, as well as pressure, on the ECs in the grafted segment from venous to arterial levels (271, 273, 301). Studies using these models have demonstrated that *1*) the flow-induced arterial dilatation is accompanied by an adaptive remodeling of the intima and requires early expression of MMPs to degrade the ECM; *2*) the NO released from ECs contributes to the increase in vessel caliber in response to a chronic increase in blood flow; *3*) high shear stress causes the release of multiple vasoregulators by ECs in addition to NO, including furin, which is a yeast Kex2-family endoprotease that converts many vasoregulatory propeptides including pro-transforming growth factor (TGF)-β to their mature forms, to modulate the functions of ECs and SMCs; and *4*) increases in shear stress induce the expression of heat shock protein 60 (252).

Larger animals such as baboons, sheep, and dogs have also been used for similar in vivo investigations on EC responses to alterations in shear stress (99, 302, 303, 309). The models of low shear stress include the decrease in blood flow by *1*) ligation of the outflow branches

(e.g., the ipsilateral internal carotid artery) or *2*) closure of an arteriovenous fistula in the rabbit or rat between the common carotid artery and the external jugular vein (29, 95, 218, 291, 300, 306, 309, 312, 378, 517, 518, 596, 624). These model studies have demonstrated that the reduction in blood flow and shear stress *1*) induces EC apoptosis and death, which may affect the arterial remodeling; *2*) reduces the flow-dependent enlargement of fenestrae in the internal elastic lamina of the arteries, which contributes to the internal elastic lamina remodeling; *3*) leads to early neointimal hyperplasia, probably due to increased SMC migration and proliferation, monocyte adhesion, macrophage infiltration, upregulation of VCAM-1, PDGFs, and MMP-9, and ECM reorganization; and *4*) induces increases in vascular oxidative stress and hence progression of experimental atheroma and angiogenesis. A recent study by Nam et al. (410) has reported that partial carotid ligation results in disturbed flow, which causes upregulation of pro-atherogenic genes, downregulation of atheroprotective genes, endothelial dysfunction, and rapid development of atherosclerosis in 2 wk and advanced lesions by 4 wk in apolipoprotein E-deficient ($ApoE^{-/-}$) mice.

B. Creation of Disturbed Flow In Vivo by Introducing a Stenosis in a Segment of a Large Artery

One of the most common strategies to create disturbed flow pattern and the associated low and reciprocating shear stress in vivo is to introduce a local stenosis in a segment of a large vessel, such as the carotid artery or abdominal aorta in rabbits or rats. Using this strategy to create a stenosis throat (40–60% reduction in diameter), Hutchison (264) found that ECs are aligned and elongated in the direction of flow up to five diameters upstream of the stenosis throat, where the flow is laminar with a relatively higher shear stress. Immediately downstream to the stenosis throat is a region of flow separation and low-velocity recirculation (identified by transcutane- ous pulsed Doppler velocimetry), and the ECs there are maximally rounded. By five diameters downstream, the ECs gradually return to the elongated shape as observed upstream. Similar results have been reported earlier by Levesque et al. (332) and Kim et al. (293), who show that in the high-shear region immediately upstream of the stenosis throat, ECs are much more elongated, and stress fibers are markedly thicker and longer than in control aortas, and that in the region of low and reciprocating shear immediately downstream of the stenosis, ECs are polygonal in shape and show a prominent peripheral band of microfilaments. Gabriels and Paul (195) report that the expression of Cx43 is locally upregulated downstream to the stenosis, suggesting that Cx43 expression can be modulated by changes in hemodynamic pattern in vivo. Miao et al. (379) demonstrate that VE-cadherin is highly expressed at EC borders in the vessel segment at sites where the blood flow is laminar; in contrast, there is little or no VE-cadherin expression in the EC borders in the poststenotic dilatation sites, where the flow is disturbed (Fig. 18). With the same experimental model, Wang et al. (600) show that KLF-2 is highly expressed in ECs in regions of laminar flow (upstream and far downstream to the stenotic throat, as well as within the throat), but there is virtually no KLF-2 expression in the ECs at the poststenotic sites with disturbed flow (Fig. 18). McCue et al. (371) have shown that the EC polarity is age- and vessel-specific in vivo and is regulated by disturbed flow. The microtubule-organizing centers (MTOCs, from which microtubules emanate) in ECs are distributed predominantly downstream of the nuclei in abdominal aortas of immature rabbits (5-wk-old) and upstream of nuclei in mature rabbits. Following the creation of a 50% stenosis of the aorta, the flow disturbance in the recirculation eddy downstream to the stenosis eliminates these EC MTOCs polarities in both immature and mature rabbits, suggesting that polarization of endothelial MTOCs in vivo is shear-dependent. These results indicate that EC structure and gene and protein expressions can be modulated by different flow patterns in vivo in a manner similar to that observed in vitro.

Cheng et al. (83) developed a perivascular shear stress modifier (a conical device with a tapered lumen, referred to as a cast) that can induce defined variations in shear stress patterns in vivo in a straight vessel segment of rabbits and transgenic mice, in which the expression and distribution of eNOS in the arterial EC can be monitored by fusion with green fluorescent protein. Placement of the cast around the carotid artery generates lowered unidirectional shear stress upstream from the cast and a downstream region of disturbed flow with reciprocating shear stress (Fig. 19*A*). The progressive stenosis of the vessel by the cast leads to a gradual increase in shear stress in the stenotic zone, reaching a maximum of 25 dyn/cm^2 at the narrowest portion (83). A strong induction of eNOS is found in the EC membrane and Golgi complex in the high-shear region around the narrowest portion of the stenotic zone, compared with the low-shear, disturbed flow regions and also the control carotid arteries that are not subjected to the treatment. The low and reciprocating shear regions show a low eNOS mRNA expression of one-third of that in the region subjected to high shear stress. En face immunostaining with antibodies against phospho-eNOS further demonstrates that the levels of eNOS phosphorylation in ECs in the high-shear region of the carotid arteries aresignificantly higher than those in the other regions. By using the same device, Cheng and co-workers (81, 82) have further demonstrated that, in addition to low and reciprocating shear stress in regions downstream to the device, low but unidirectional laminar flow in regions upstream to the deivce is also atherogeneic. They found that atherosclerotic lesions develop under conditions of both unidirectional flow with low shear stress and disturbed flow with reciprocating shear stress within 6 wk of cast placement, whereas no lesions develop in the high shear stress region (Fig. 19*B*). The low unidirectional shear stress upstream of the cast induces the development of extensive lesions with a more inflammatory and vulnerable- plaque phenotype, whereas disturbed flow with low and reciprocating shear stress downstream of the cast induces the growth of stable lesions. Using angiotensin II administration, Cheng et al. (82) have shown that intraplaque hemorrhages occur exclusively in the atherosclerotic lesions of low unidirectional shear stress regions. However, this difference should be interpreted with caution, since one would predict that with a severe constriction, the upstream region would have higher blood pressure than the downstream region (242), and hence one cannot interpret these results solely in terms of flow patterns. In any event, reduction in flow and shear stress is associated with sustained inflammatory signaling in ECs, as well as their failure to align with flow.

In *tie1-lacZ* transgenic mice, Porat et al. (469) have shown that the expression of the *tie1* promoter in the arterial tree is enhanced in vascular bifurcations and branch points, i.e., regions of disturbed flow. Flow disturbance induced by the surgical interposition of a vein into an artery leads to an induction of *tie1* expression in the region immediately downstream of the artery-to-vein junction, where the lumen enlargement of the grafted vein due to exposure to arterial pressure provides a geometry analgous to poststenotic dilatation. This *tie1* induction by flow disturbance in vivo is confirmed by in vitro study using a step-flow channel, where the upregulation of *tie1* promoter activity is seen only in ECs residing in the region of flow separation and recirculation downstream to the step (469).

C. In Vivo Observations of EC Signaling and Gene Expression at Athero-prone Areas

Most of the in vitro studies using flow chamber on the effects of disturbed flow on EC signaling, gene expression, and functional modulation have been confirmed by in vivo observations at athero-prone regions of the arterial tree, e.g., carotid bifurcations, aortic arch, and curvatures and tortuosities of coronary arteries (Table 3). For example, ECs in athero-prone areas, i.e., regions of disturbed flow with low and reciprocating shear stress, show increases in mitotic rate (86), lipid uptake (507), and monocyte adhesion (596), which are accompanied by the changes in EC morphology and structure (57) and increases in the expression or activation of ICAM-1 (112, 168, 269, 407, 537, 552), VCAM-1 (168, 269,

407, 552, 596) (Fig. 20), E-selectin (168), PDGFs and their receptors (309, 566, 616), Cx43 (195, 314), Egr-1 (369), Ang-2 (574), cathepsin K (461), NF-κB (48, 100, 234, 620), MMPs (29, 218), p70S6K (228), TLR-2 (399), PAK (437, 440), Shc (350), JNK (229), XBP-1 (647), HuR (487), GTPCH-1 (335), and HDAC3 (643), and decreases in AMPK (228) and Nrf2 (116), compared with the straight segments, where the blood flow is laminar and unidirectional. MCP-1 protein expression examined by immunocytochemistry has shown a preferential expression near the intercostal artery orifices compared with the straight part of the aorta (86); mapping of monocyte distribution in the aorta also shows that there is a preferential localization at branch points (362). Both BMP-2 and BMP-4, which are induced by low and reciprocating shear stress (537), are found in atherosclerotic plaques and calcified aortic valves (46, 151, 389), suggesting their importance in the development of atherosclerotic diseases. ECs overlying foam cell lesions express BMP-4, but nondiseased ECs do not (537). Interestingly, BMP-4 antagonists follistatin, noggin, and matrix Gla protein are also highly expressed in mouse aortas and human coronary arteries (71). Chronic infusion of BMP-4 causes endothelial dysfunction in a vascular NADPH oxidasedependent manner and induces hypertension in mice (385). BMP-4 stimulates the expression and activity of NADPH oxidase through $p47^{phox}$ and Nox-1 in an autocrine-like manner (536, 537), leading to ROS production, NF-κB activation, ICAM-1 expression, and subsequent increases in monocyte adhesion to ECs (279, 536, 537).

ECs rely on specific ECM-integrin interactions to mediate both “inside-out” and “outside-in” signaling communications with ECM (521, 522). For example, the integrins $\alpha_1\beta_1$ and $\alpha_2\beta_1$ interact with collagen, whereas $\alpha_5\beta_1$ and $\alpha_v\beta_3$ bind to fibronectin. There is little fibronectin or fibrinogen beneath the endothelium in most of the vasculature, but these proteins are found at sites of disturbed flow in vivo (439). Deletion of an alternatively spliced domain of fibronectin that reduces its assembly into matrix decreases atherosclerosis in hypercholesterolemic $ApoE^{-/-}$ mice (562). Thus ECM remodeling with fibronectin and/or fibrinogen deposition in disturbed flow regions may induce an activated EC phenotype in these regions and promote atherosclerosis. In concert with these in vivo findings, in vitro studies have shown that the activations of NF-κB (439), PAK (440), and JNK (229) at the onset of laminar flow and/or long-term reciprocating flow is ECM-dependent, with enhanced activity in ECs seeded on fibronectin or fibrinogen, rather than basement membrane protein laminin or collagen. Higher levels of phosphorylated NF-κB, PAK, and JNK are present in athero-prone than in atheroprotective areas of C57BL/6J and $ApoE^{-/-}$ mice (229, 437, 439, 440). Knockout of JNK2, but not JNK1, decreases lesion development in $ApoE^{-/-}$ mice (488). On the other hand, injecting mice with the PAK-Nck inhibitory peptide reduces vascular permeability at athero-prone sites (440). Inhibiting PAK in ECs on fibronectin blocks the NF-κB and JNK activations by both laminar and reciprocating flows in vitro or at sites of disturbed flow in vivo, suggesting that NF-κB and JNK activations by flow are mediated by PAK (229, 437). In addition, these flow activations of NF-κB and JNK in ECs on different ECM proteins are mediated by different integrins. Thus, while the flow activation of NF-κB is prevented by the ligation of $\alpha_2\beta_1$ integrin on collagen through a p38 MAPK-dependent pathway (439), the flow activation of JNK in ECs seeded on fibronectin is inhibited by blocking $\alpha_v\beta_3$ integrin/fibronectin signaling with anti-$\alpha_v\beta_3$ monoclonal antibody LM609 (275) or anti-fibronectin antibody 16G3 (229). A mechanosensory complex consisting of the immunoglobulin family receptor platelet endothelial cell adhesion molecule (PECAM)-1, the tyrosine kinase VEGF receptor-2 (VEGFR-2), and VE-cadherin at the endothelial junctions may serve as an upstream signaling complex for ECM-integrin activation in response to flow (229). Through this complex, flow activates phosphatidylinositol (PI) 3-kinase, and the increased level of PI lipids then changes the affinity of integrins such as $\alpha_5\beta_1$ and/or $\alpha_v\beta_3$.

The signaling induced by integrin activation must be transmitted into cells through the activation of integrinassociated proteins such as Shc, an adaptor protein containing a COOH-terminal Src homology domain-2 domain, which subsequently activates several intracellular signaling cascades, including JNK and p38 MAPK (522). Shc activation occurs in vivo and correlates with areas of disturbed flow and atherogenesis (350). The association of Shc with integrins requires VE-cadherin, and the activation of Shc requires VEGFR-2 and Src, a tyrosine kinase that localizes to EC junctions in response to mechanical force (350, 602). Moreover, Shc regulates flow-induced ICAM-1 and VCAM-1 by activating NF-κB-dependent signals that lead to atherogenesis (350). A recent study by Funk et al. (193) on human and bovine aortic ECs shows that basement membrane proteins enhance the flow-induced activation of PKA, which suppresses PAK. Activating PKA by injecting the prostaglandin 2 analog iloprost reduces PAK activation and ICAM-1 and VCAM-1 expressions at sites of disturbed flow in vivo (i.e., the outer wall of the carotid sinus in C57BL/6J mice), whereas inhibiting PKA inhibition stimulates PAK activation and inflammation in vivo. Thus basement membrane proteins inhibit proinflammatory signaling in ECs via PKA-dependent inhibition of PAK (193). Taken together, these results indicate that integrin-ECM is mechanosensitive and that the types of ECM in the subendothelial space would determine the responsiveness of ECs to the imposed flow patterns (521). In addition, a dynamic interaction between integrins and their cognate ECM proteins is a very early event in mechanotransduction in ECs responding to different patterns of flow and associated shear stress (521).

Endothelial glycocalyx, a carbohydrate-rich layer that is a network of membrane-bound proteoglycans and glycoproteins lining the luminal side of endothelium, may serve as a mechanosensor to transmit mechanical forces into biochemical signals in ECs (181, 470, 608, 610, 635). In healthy mice, a thinner glycocalyx is found in the internal carotid sinus region compared with the common carotid artery (73 ± 36 vs. 399 ± 174 nm) (484, 586). After 6 wk of atherogenic diet, the glycocalyx size is significantly decreased in the mouse carotid artery; at the same time, evidence of enhanced atherosclerotic plaques are observed in these mice (586). Impaired barrier properties of glycocalyx contribute to the enhanced LDL accumulation in intima at the carotid artery bifurcation in mice (587). These results suggest that flow patterns and associated shear stresses may play important roles in modulating glycocalyx dimensions and that endothelial glycocalyx may serve an atheroprotective function (428, 484). In vitro studies on ECs treated with heparinase III to specifically break down heparan sulfate proteoglycans in the glycocalyx (181) and ex vivo examinations on canine femoral arteries infused with hyaluronidase to degrade hyaluronan glycosaminoglycans in the glycocalyx (386) show significant reductions in shear-induced NO production, indicating that both heparan sulfate and hyaluronan in the endothelial glycocalyx are critical for sensing flowinduced shear forces on ECs. Interestingly, exposure of ECs to laminar shear stress (10 dyn/cm^2) increases the amount of glycocalyx hyaluronan by twofold of static controls, which may represent a positive feedback for shear stress sensing by ECs (221).

An additional mechanosensor that is regulated by different flow patterns is endothelial primary cilium, which is an integral component of apical membrane organelles on ECs. Endothelial primary cilium is present in areas of low and disturbed flows in the embryonic cardiovascular system (588) and the adult aortic arch of wildtype C57BL/6J and ApoE$^{-/-}$ mice (589). Placement of a restrictive cast on the common carotid artery to create low and disturbed flow regions results in the presence of primary cilia only at these sites (589). In the early stage of arterial development, a shear-dependent distribution of primary cilia is present, coinciding with the expression of shear-related genes, including KLF-2, ET-1, and eNOS (225, 588). These genes respond to alterations in vascular shear stress in embryonic and adult models (80, 83, 226). In the heart, ciliated endocardial cells are only present in

areas of disturbed flow, such as the atrial and ventricular chambers, and are absent from high-shear areas such as the atrioventricular canal and outflow tracts from the ventricles (462). These results suggest that the mechanosensing proteins in the cilia may play important roles in modulating signaling and gene expression in ECs and the consequent modulation of EC/vascular functions in response to disturbed flow.

The expression of complement inhibitory protein CD59 on vascular endothelium is significantly higher in the athero-resistant regions of the murine aorta exposed to unidirectional laminar shear stress, compared with the athero-prone areas exposed to disturbed flow (296); this is significant because complement activation may predispose blood vessels to injury and atherogenesis (508). Protein kinase C (PKC)-ζ activity has been shown to correlate with flow patterns in pig arteries, being higher in ECs exposed to disturbed flow than to unidirectional laminar flow (356). MKP-1 has been found by immunostaining to be preferentially expressed by ECs in a highshear, atheroprotected region of the mouse aorta, and to be necessary for the suppression of EC activation at this site, since its genetic deletion enhances p38 activation and VCAM-1 expression (642). Nitrotyrosine, which is considered to be an emerging inflammatory marker for atherosclerosis and a fingerprint of peroxynitrite (a product of superoxide anion reacting with NO), shows positive immunostaining in human coronary artery bifurcations or curvatures, but absence in the straight segments (258, 515). Connective tissue growth factor (CTGF), a potent angiogenic, chemotactic, and ECM-inducing growth factor, is overexpressed in atherosclerotic arteries (433) and strongly upregulated by nonuniform shear stress in ECs (637), suggesting that disturbed flow at arterial bifurcations may induce EC CTGF expression to contribute to the progress of atherosclerotic lesions. Phosphorylated nuclear activated transcription factor-2 (ATF-2), which is one of the heterodimeric components of transcription factor activator protein-1 and is crucial for cytokine-induced expression of E-selectin in ECs (90, 383, 480), is present in human ECs overlying atherosclerotic plaques at higher levels than ECs at unaffected sites; in cultured ECs, the ATF-2 activation in the EC nuclei is inhibited by laminar shear stress (180). Endothelial vWF shows substantial heterogeneity in its distribution throughout the vasculature (479), with higher levels found at sites such as branch points, bifurcations, and curvatures (19, 479, 629).

In concert with the reduced KLF-2 expression in ECs at sites of disturbed flow, as presented for in vivo and in vitro model systems (see sects. **IV***D* and **V***B*; Fig. 18), decreased KLF-2 expression is found at the human aortic bifurcations and the branch points of iliac and carotid arteries, coinciding with the sites of neointima formation (145). The direct involvement of shear stress in the in vivo expression of KLF-2 is demonstrated by in situ hybridization and laser microbeam microdissection/reverse transcriptase- polymerase chain reaction in a murine carotid artery collar model, in which a 4- to 30-fold induction of KLF-2 occurred at the high-shear sites (145). Lee et al. (329), using zebrafish and KLF-2-deficient mouse models, demonstrate that KLF-2 expression during development mirrors the rise of fluid shear forces and that endothelial loss of KLF-2 results in lethal embryonic heart failure. Fluid shear stress drives expression of endothelial KLF-2 that, in turn, regulates smooth muscle tone in the developing embryo (329). These results suggest that KLF-2 is an essential regulator of vascular hemodynamic forces in vivo and that hemodynamic regulation in response to fluid shear stress is required for cardiovascular development and function.

To discriminate the gene expression profiles of ECs between sites of disturbed flow and laminar flow in vivo, Passerini et al. (450) have conducted DNA microarray study on fresh ECs isolated from regions of inner aortic arch (areas exposed to disturbed flow) and descending thoracic aorta (areas exposed to laminar flow) of normal adult pigs. In the inner

aortic arch, there is an upregulation of several inflammatory cytokines and receptors, as well as elements of the NF-κB system, which reflects a proinflammatory phenotype. This proinflammatory phenotype is probably mediated by PECAM-1, because PECAM-1-knockout mice do not exhibit activation of NF-κB and the downstream inflammatory genes in regions of disturbed flow (239, 581). Goel et al. (219) have shown that PECAM-1 has both atherogenic and atheroprotective effects, but that the former dominates in the inner curvature of the aortic arch, whereas the latter dominates in the aortic sinus, branching arteries, and descending aorta. In this connection, the regional DNA microarray study by Passerini et al. (450) has shown that some of the atheroprotective profiles found primarily in laminar flow regions are also seen in disturbed flow regions, notably the enhanced expression of antioxidant genes. Thus the gene expression profile in disturbed flow regions may reflect a delicate balance between atherogenic and atheroprotective genes; the action of risk factors may tip the balance to initiate atherogenesis (450).

D. Experimental Model Studies on Venous Inflammation and Thrombosis Induced by Disturbed Flow With Venous Hypertension

Venous reflux through incompetent venous valves or stasis is a major cause of venous hypertension that underlies many, and possibly all, clinical manifestations of primary chronic venous diseases. There are at least three types of animal models that have been used to investigate the mechanisms by which the disturbed flow (i.e., reflux or stasis) associated with venous hypertension triggers inflammatory processes in chronic venous diseases (35). These models include *1*) occlusion of a mesenteric venule in rats to allow direct observation of events occurring early after the onset of disturbed flow with increased venous pressure (35, 556–558); *2*) placement of an arteriovenous fistula between the femoral artery and vein in the groin of the rat to investigate the effects of disturbed flow and venous hypertension over a longer time scale and in larger veins (35, 447, 449, 559, 560); and *3*) ligation of large veins (e.g., inferior vena cava, common femoral veins, and common iliac veins) to investigate the link between disturbed flow with venous hypertension and the skin changes and thrombosis that are important manifestations of severe chronic venous diseases (35, 36, 231, 232, 320).

The venular occlusion experiments show that reduction in flow and shear stress can rapidly set in motion an inflammatory cascade, including hallmarks like WBC adhesion to the endothelium and migration into the interstitium, ROS production, and parenchymal cell death that begins immediately after occlusion and continues for at least 1 h after the release of the occlusion and reperfusion (35, 558, 619). Occlusion of a mesenteric venule also induces a significant increase of pressure upstream of the occlusion, which enhances the magnitude of the inflammatory reactions (35, 558). The formation of a femoral arteriovenous fistula induces an immediate increase in venous pressure followed by a detectable reflux, which mirrors the progressive changes in venous valve morphology and leads to, in some cases, the complete disappearance of valvular structures (35). Pressurized valves show increased numbers of granulocytes, monocytes/marcophages, and T lymphocytes and elevated levels of P-selectin and ICAM-1 in the endothelium compared with control valves. The expression of MMP-2 is increased mostly in the subintima and the media of the venous wall and in the subendothelial connective tissue of the valvular leaflets, whereas MMP-9 is mostly expressed in the intima and subintima of both the venous wall and valvular leaflets (449). Experiments using the large vein ligation model of disturbed flow with venous hypertension show that these hemodynamic alterations result in elevated levels of tissue WBCs (231, 320), which can be prevented by prior injection of an anti-ICAM-1 monoclonal antibody (232), suggesting a role of ICAM-1 in WBC adhesion and migration in skin tissues, as well as in the walls and valves of large veins.

The inferior vena cava ligation in animals (e.g., mice, rats, cats, and baboons) to produce venous stasis induces thrombus formation and deleterious changes in venous valves and vein walls (158, 401–403, 593, 594). This stasis-mediated induction of venous thrombosis requires concomitant changes in EC function and/or activation of clotting (248). Thrombus initiation is associated with a rapid inflammatory reaction in the vein wall involving early neutrophil infiltration (157) and a later wall remodeling associated with increased MMP-9 and MMP-2 expressions (141). Animal model studies indicate the roles of P-selectin, E-selectin, TF, VEGF, basic fibroblast growth factor (bFGF), and microparticles released from WBCs in modulating stasis-induced venous thrombosis (137, 401, 404, 550, 598). For example, compared with wild-type mice, mice that are null for P-selectin, E-selectin, or TF show markedly reduced thrombus formation after inferior vena cava ligation (137, 401, 404, 550). Inhibition of P-selectin using its oral small molecule inhibitor PSI-697 reduces vein wall injury (402), and administration of an anti-P-selectin antibody or a recombinant soluble form of P-selectin glycoprotein ligand-1 (PSGL-1) inhibits stasis-induced inflammation and thrombus formation (158, 169, 593). Transplantation of wild-type bone marrow into low-TF mice does not accelerate venous thrombus formation (137). Similarly, transplantation of low-TF bone marrow into wild-type mice does not suppress venous thrombus formation. These results suggest that the stasisinduced thrombus formation in the venous macrovasculature is driven primarily by TF derived from the blood vessel wall rather than circulating WBCs (137). It has been proposed that in deep venous thrombus, TF- and PSGL-1-bearing microparticles arising from cells of monocyte/ macrophage lineage can bind to either P-selectin or E-selectin on the stasis-activated ECs in regions of vessel activation or inflammation to initiate clotting cascade (8, 351). The importance of microparticles, TF, and P-selectin/ E-selectin in venous stasis-induced thrombosis has also been shown in the developing thrombus in mouse arterioles induced by endothelial injury model (173). In addition, it has been demonstrated that CXCR2 and CCR2, the receptors for cysteine-X-cysteine (CXC) and cysteinecysteine (CC) chemokines that are highly expressed in vascular ECs, play important roles in modulating stasisinduced thrombus formation in the mouse inferior vena cava ligation model (246, 247).

The results drawn from the experimental animal model studies on the role of disturbed flow in the pathogenesis of chronic venous diseases are comparable with the examinations of affected veins from patients with chronic venous diseases, which show *1*) increased monocye/ macrophage infiltration of the valvular leaflets and venous wall (436); *2*) elevated ICAM-1 expression in the vein wall and valves (555); *3*) increased levels of ICAM-1, VCAM-1, and E-selectin in plasma, suggesting endothelial activation (274, 497); *4*) greater levels of activation of circulating WBCs and elevated ROS production in plasma (561); *5*) increased numbers of macrophages, lymphocytes, and mast cells in skin biopsies (443, 617); *6*) elevated levels of mast cell infiltration, suggesting that inflammation may be a cause rather than a consequence of venous disease (280, 630); *7*) increased ratios of TIMP-1/ MMP-2 and TIMP-2/MMP-2 (3.6 and 2.1 times, respectively) and elevated levels of cytokines TGF-β1 and bFGF in the walls of varicose veins compared with control subjects, which could favor the accumulation of ECM in varicose veins (18); *8*) higher plasma levels of VEGF and PDGF compared with control subjects (380, 519); and *9*) higher plasma levels of MMP-9 in patients with varicose veins in response to postural blood stasis (274). Most of these events occurring in patients with chronic venous diseases are also present in the formation and progression of atherosclerotic lesions, indicating a common role played by disturbed flow in the pathogenesis of arterial and venous diseases.

VI. ENDOTHELIAL HETEROGENEITY AND ITS PATHOPHYSIOLOGICAL BASIS FOR DISTURBED FLOW-RELATED VASCULAR PATHOLOGIES

ECs from different anatomical locations demonstrate a remarkable heterogeneity in both structure and function under normal and pathological conditions (5, 6). The notion of phenotypic diversity of ECs arises from both in vivo (510, 538) and cell culture studies (60, 84, 146, 567), which indicate that there are substantial differences in gene expression between ECs from different vascular sites. These differences in gene expression and phenotypes in ECs from different vascular beds may account for specific susceptibility of vascular beds to pathological conditions, including disturbed flow with altered shear stress (7). For example, while vWF is expressed at the significantly higher levels in venous ECs than arterial ECs (631), eNOS is mainly expressed in the arterial side of the circulation (15, 468). TNF-α is able to activate NF-κB and activated protein-1 in both human umbilical artery and vein ECs, but can cause inductions of VCAM-1 and E-selectin only in human umbilical vein ECs (347). ICAM-1 is induced in both cell types, but at a higher level in umbilical venous than arterial ECs (347). Freshly isolated umbilical arterial ECs express higher levels of KLF-2 than umbilical venous ECs, and the fall in KLF-2 expression when umbilical arterial ECs are placed in cell culture correlates with a gain in TNF-α responsiveness (347). In vivo studies on adhesion molecule expression and WBC adhesion in the mouse aorta and inferior vena cava using intravital microscopy and immunostaining have demonstrated that venous ECs have a greater capacity to mount an inflammatory response than arterial ECs (8, 171). It is possible that the proinflammatory properties of venous ECs influence the development of venous thrombosis and vein graft atherosclerosis in which inflammatory responses play major roles (130, 171, 593). By using DNA microarray technique to analyze 52 purified EC samples from 14 distinct locations, Chi et al. (84) have demonstrated that significant transcriptional differences exist between cultured arterial and venous ECs, e.g., arterial ECs have higher levels of CD44 and endothelial lipase, a member of the triglyceride lipase gene family, than venous ECs. This difference is in accordance with the finding that arterial and venous ECs are derived from separate sets of embryonic precursor cells with distinct gene expression profiles (327). The notion that the higher levels of CD44 and endothelial lipase in arterial ECs may underlie the preferential arterial involvement of atherosclerosis (84) is supported by the findings that disruption of CD44 in mice results in a dramatic decrease in atherosclerosis (110) and that an elevated level of endothelial lipase is associated with reduced highdensity lipoprotein and increased atherosclerosis (96, 272). By exposing human saphenous vein and coronary artery ECs to venous-like (2.2 dyn/cm^2, steady flow) and coronary artery-like (17 ± 1.4 dyn/cm^2, 1 Hz) flow patterns in a custom Silastic tube perfusion system (22), Methe et al. (377) have demonstrated that arterial and venous ECs respond differentially to different flow patterns and shear stresses. While both flow patterns have no effect on VCAM-1 and E-selectin expressions in these two types of ECs, ICAM-1 regulation by flow is more complex. Coronary artery-like flow induces a higher level of ICAM-1 expression in human coronary artery ECs than that induced by venous-like flow. In contrast, the expression of ICAM-1 in human saphenous vein ECs exposed to coronary artery-like flow is lower than that exposed to venouslike flow. However, both flow patterns induce higher levels of ICAM-1 expression in human saphenous vein ECs than in human coronary artery ECs. These results indicate that flow-dependent regulation of ICAM-1 expression differs markedly between arterial and venous ECs (377).

Endothelial heterogeneity between straight and branched parts of the arterial system or among different arteries may influence the athero-susceptibility of different arteries. For example, TF is virtually undetectable in normal endothelium in the arterial system, but in a baboon sepsis model in which lethal doses of *Escherichia coli* are intravenously injected, TF

is expressed at higher levels in the arterial branches than in the straight segments of aorta, suggesting that sitedependent endothelial heterogeneity contributes to focal pro-coagulant responses to septic stimuli under disturbed flow (8, 353). A human biopsy study by Dalager et al. (117) suggests that the initiation, development, and composition of atherosclerotic plaques differ among arteries in different regions. The coronary arteries have a higher prevalence of atherosclerotic plaques compared with the carotid and femoral arteries. ECs derived from coronary arteries of male New Zealand rabbits have significantly lower eNOS mRNA levels and a stronger pro-atherogenic gene expression pattern compared with aortic ECs (118). Zhang et al. (650) demonstrate the EC heterogeneity between typical athero-prone and athero-resistant arteries in vivo by comparing gene expression profiles of ECs isolated from freshly harvested porcine coronary versus iliac arteries with the use of DNA microarrays. The in vivo transcriptional difference between these two types of ECs has provided insights into the factors responsible for coronary artery athero-susceptibility. Systematic identification of molecular biomarkers for ECs from specific vessels or vascular beds will not only enhance our understanding of the mechanisms underlying endothelial heterogeneity of different vascular beds and its pathophysiological basis for vascular disorders, but may also provide the potential for site-specific delivery of therapeutic agents.

VII. FLOW-RELATED SIDENESS OF VALVULAR ENDOTHELIAL PHENOTYPE AND ITS PATHOPHYSIOLOGICAL SUSCEPTIBILITY

There is increasing evidence that endothelium plays a critical role in the pathogenesis of valvular heart disease and that aortic valve stenosis is associated with systemic endothelial dysfunction, with the characteristics of the atherosclerotic process (328, 463). Aortic valve diseases preferentially occur on the aortic side of the valvular leaflets where they are exposed to complex flow patterns (432, 441). However, the contributions of valvular endothelial phenotypes to this sidespecific response potentially associated with the local flow environment have not been fully clarified. The exposure of valvular ECs to unidirectional laminar shear stress results in the alignment of these ECs perpendicularly to the direction of flow, in contrast to the parallel alignment of vascular ECs to flow (58, 59). Comparison of transcriptional profiles of valvular versus vascular ECs under static and shear stress conditions shows that up to 10% of the genes considered in that study are significantly different (60), suggesting clear phenotypic differences between these two cell types in response to shear stress. Despite these differences, the pathological inflammatory responses of the two cell types involve similar mediators such as ICAM-1, VCAM-1, and E-selectin (398). In the context of the valvular response, these mediators are expressed preferentially on the aortic side of the leaflets. Using RNA amplification and DNA microarrays, Simmons et al. (529) identified 584 genes that are differentially expressed in situ by the endothelium on the aortic side versus ventricular side of normal adult pig aortic valves. These differential transcriptional profiles, representative of the steady state in vivo, identify globally distinct endothelial phenotypes on opposite sides of the aortic valve. Several inhibitors of cardiovascular calcification are less expressed by endothelium on the disease-prone aortic side of the valve, suggesting side-specific permissiveness to calcification. Sucosky et al. (548) demonstrate the involvement of BMP- and TGF-β1-dependent signaling events are involved in aortic valve inflammation, which occurs preferentially on the aortic side of the valvular leaflets. These ex vivo findings implicate that complex flow conditions in the aortic side of the valvular leaflets may regulate valvular endothelial signaling, gene expression, and phenotype to contribute to the preferential susceptibility to lesion development in this region.

Venous valves are frequent sites of venous thrombosis initiation. However, the possible contribution of the valvular sinus endothelium to the intiation of venous thrombosis has received little attention. Using immunofluorescence staining to examine great saphenous

veins harvested at cardiac bypass surgery, Brooks et al. (52) have demonstrated an upregulation of anticoagulant and downregulation of procoagulant activities in the endothelium of venous valve sinus (i.e., the distal side of valvular leaflets) compared with that of vein lumen (i.e., the proximal side of valvular leaflets). The expressions of endothelial protein C receptor and thrombomodulin, both of which facilitate the thrombininduced activation of protein C in the anticoagulant and anti-inflammatory pathways, are higher in the endothelium of valvular sinus than those in the endothelium of vein lumen. In contrast, the expression of vWF is lower in the sinus endothelium than the vein luminal endothelium. These results suggest that valvular sinus endothelium may maintain a thromboresistant phenotype to play homeostatic roles in protecting against venous thrombogenesis (8, 52).

VIII. CLINICAL APPLICATIONS AND PERSPECTIVES

We have discussed in this review the physiological and pathophysiological relevance of the effects of disturbed flow and its associated shear stress pattern on vascular ECs. The results of studies on this subject have significant applications and implications in several fields of clinical medicine and surgery related to vascular diseases. The clinical applications based on these concepts include the following: *1*) maintenance and enhancement of shear stress to improve endothelial/vascular functions in patients undergoing vascular surgery; *2*) minimization of regions of disturbed flow created by surgical interventions and host-prosthesis mismatch; *3*) augmentation of blood vessel formation by modulation of shear stress; *4*) development of gene therapy strategies and antiatherogenic drugs that take into account the shear stress- responsive targets; and *5*) prevention of reflux and venous hypertension to alleviate symptoms of chronic venous diseases

A. Maintenance and Enhancement of Shear Stress to Improve Endothelial/Vascular Functions

Neointimal hyperplasia is a critical process leading to atherosclerosis and restenosis, as well as their complications. Since high shear stresses with a significant net direction can result in a reduction in neointimal hyperplasia, several strategies have been designed to modify shear stress to increase vascular patency following surgical interventions such as bypass graft and stenting. Thus a distal arteriovenous fistula has been used to increase blood flow and shear stress above a critical threshold to prevent thrombosis and neointimal hyperplasia of the graft, with the goal of improving the patency of bypass graft that had poor outflow (120, 121, 442, 472). Seeding of prosthetic bypass grafts with an EC monolayer reduces thrombosis and improve patency; application of a physiological level of laminar shear stress to such grafts increases the adhesion of seeded ECs and enhances their retention after implantation in vivo, thereby improvng graft patency (418, 429). Carlier et al. (67) have shown that the insertion of a flow divider (Anti-Restenotic Diffuser, Endoart) in a stent placed in the external iliac arteries of rabbits on a hypercholesteremic diet increases the shear stress to result in a local reduction in neointimal hyperplasia and the consequent prevention of in-stent restenosis. In addition to these applications of shear stress modifications to improve vascular patency following surgical interventions, there is evidence that exercise training can improve endothelial function and is beneficial to the treatment and prevention of cardiovascular diseases (98, 160, 426, 427). Exercise-induced increases in flow and shear stress also enhance the expression of eNOS and production of NO by ECs (238, 582) to increase myocardial perfusion, with the consequent retardation of progression, or even facilitation of regression, of coronary artery disease (505). In addition, the increase in shear stress and flow magnitude may move the stagnant zone and reattachment point downstream so that the athero-prone region will not be constantly exposed to the disturbed flow. This is probably why exercise needs to achieve a certain degree of intensity, maintain a certain duration of time, and sustain with a certain regime of

regularity. All of these will help to move the stagnation, reattachment points downstream away from the disease-prone areas which would have stayed at the same place in a sedentary situation.

B. Minimization of Disturbed Flow Regions Created by Surgical Interventions and Host-Prosthesis Mismatch

In vascular surgery, it is crucial to avoid mechanical and geometrical changes that may result in large flow disturbances and the consequent thrombosis and restenosis. Studies on bypass surgery have demonstrated that the graft angle at the distal anastomosis is one of the determinants of shear stress and flow pattern (113, 340, 343, 513, 539). A sharp degree of angulation contributes to the formation of complex flow patterns and areas of low shear stress within the anastomosis (113, 539), leading to thrombosis and restenosis, and hence graft failure. Several types of anastomotic cuffs or patches have been developed to reduce the compliance mismatch between the artery and the graft, with the aim of minimizing areas of disturbed flow and low shear stress, thus improving bypass graft patency (113, 178, 297, 310, 340, 381, 419, 546). When a saphenous vein graft is used, valvulotomy of venous valves before coronary artery bypass allows a more even flow and thus avoids a potential cause for thrombus formation and graft failure (382). It is beneficial to reinforce the saphenous vein prior to grafting to prevent the occurrence of mechanical mismatch between the vien graft and the host artery (86, 348). Clinical evidence has suggested that the patency rate of small grafts is improved by matching the elastic properties of the graft to that of the host artery (340). Thus it is important to consider the mechanical and geometrical matching between the graft and the host vessel to prevent the creation of complex flow patterns due to host-prosthesis mismatch. It has been repeatedly shown that there is a link among stent design (165, 167, 288), implantation strategy (10, 167, 287), and clinical outcome, and also between wall shear stress and neointimal formation, thrombosis, reendothelialization, and restenosis (298, 543, 544). The flow separation zones induced by stent struts can be reduced in size or eliminated by the incorporation of fluid dynamic theory into stent strut design, suggesting that strut streamlining will prevent complex flow conditions that would lead to local inflammation and coagulation associated with stents (277). In addition to stent deployment, cardiac surgeons and cardiologists also need to address the optimization of hemodynamic performance in aortic valve replacement surgeries.

C. Augmentation of Blood Vessel Formation by Modulation of Shear Stress

Patients undergoing bypass surgery and angioplasty tend to suffer from risks such as restenosis and neurological complications (420). To counter this problem, a new approach for the treatment of arterial oc- clusive disease has been proposed to restore blood flow of affected area by stimulating the growth of collateral vessels, viz. “arteriogenesis,” to bypass the sites of arterial lesions (241). Shear stress plays a significant role in arteriogenesis. Under physiological conditions, almost no net blood flow is present in preexisting collateral anastomoses. Stenosis or occlusion of a major artery can induce dramatic changes in the local circulation and the local blood pressure, which tend to increase the shear stress within the collateral network as a compensatory mechanism to activate the collateral endothelium. This would lead to the recruitment of circulating blood monocytes and bone marrow-derived cells and the proliferation of vascular cells, thus facilitating arteriogenesis. In general, collateral arteries cannot completely restore the physiological level of arterial blood flow, and the growing process would stop at a stage of partial adaptation (241). Several approaches, including gene and cell therapies, have been tested with the aim of augmenting arteriogenesis (486). Novel knowledge gained from studies on EC responses to changes in shear stress may be applied to designing new biochemical and mechanical therapeutic strategies to enhance arteriogenesis (486).

D. Development of Gene Therapy Strategies and Anti-atherogenic Drugs That Take Into Account Shear Stress-Responsive Targets

Increases in our understanding of how ECs respond to disturbed flow and changes in shear stress can lead to breakthroughs in the design of novel therapeutic strategies for gene therapy and anti-atherogenic drugs. For example, Bryant et al. (54) have shown that the delivery of Egr-1, which is highly responsive to shear stress, promotes angiogenesis and tissue repair in vivo. Jin et al. (278) and Wu et al. (627) have tested the possibility of using the negative mutant of Ras (an upstream signaling molecule of MAPK), i.e., RasN17, to prevent the vascular stenosis induced by balloon injury in animal experiments. With the delivery of adenoviruscarrying RasN17, the wall thickening following balloon injury is markedly attenuated, with sufficient widening of the lumen to allow an essentially normal flow (Fig. 21). Houston et al. (255) have developed hybrid vectors that contain the luciferase reporter gene with the shear stress-responsive element (with the nucleotide sequence of "GAGACC") in the promoter region. Instillation of these vectors in vivo into the left carotid artery of rabbit and subsequent generation of a stenosis using a mechanical wire occluder results in a 10-fold upregulation of luciferase reporter gene expression at the sites of vessel occlusion, compared with the unstenosed sites. These vectors show promise for use as a carrier of therapeutic genes for gene therapy of vascular occlusive disease. Laminar shear stress induces the EC expression of eNOS and productions of NO and superoxide dismutase (which reduces oxidative degradation of NO); such shear-induced effects would be beneficial since antioxidants or the NO precursor L-arginine can improve endothelial function, enhance coronary blood flow, reduce angina, and improve exercise tolerance in patients with coronary artery disease (331). These examples illustrate how basic research on EC responses to shear stress and disturbed flow can generate new approaches for the development of strategies for gene therapy and anti-atherogenic drugs for clinical management of vascular disease.

E. Prevention of Venous Stasis and Reflux to Alleviate Symptoms of Chronic Venous Diseases

Clinical treatments for chronic venous diseases generally aim to prevent venous stasis, reflux, and venous hypertension, as well as their induced inflammation, which can alleviate symptoms of chronic venous diseases and reduce the risk of ulcers, thereby improving the quality of life. Standard therapies for varicose veins are exercise, weight loss, blood pressure control, and compression stockings. Exercise with foot movements may increase the velocity of main stream of venous flow, thus reducing the pressure on the luminal side of the valvular leaflets to cause closure of the valve; this would minimize the reflux and prevent the exposure of endothelial surfaces to reverse blood flow (36). Compression stockings are clinically effective to improve venous hemodynamics and reduce edema in patients with chronic venous diseases, but they may not be usable for a wide variety of reasons, including application difficulty (because of frailty or arthritis), physical constraints (e.g., limb obesity, contact dermatitis, or tender, fragile, or weepy skin), and coexisting arterial insufficiency (268, 478). Recent advances in surgerical research suggest that surgical procedures such as saphenous ablation or stent replacement to correct venous reflux or obstruction can aid rapid healing and prevent the recurrence of ulcers, with the reduction in or discontinuation of the use of compression stockings afterwards (413, 414, 478). In addition, treatment with agents that reduce oxidative stress by scavenging ROS or inhibit the inflammatory cascade may prevent the progressive deterioration of the valves and wall of the affected veins and hence reduce the reflux (35). For example, animal experiments show the occurrence of significant attenuation in the distortion of valves in affected veins and reduction in the rate of reflux in response to the administration of micronized purified fraction of flavonoid in a dose-dependent manner (35); flavonoid is a naturally occurring antioxidant substance that can scavenge superoxide anions and lipid peroxy radicals (3, 490) and reduce WBC adhesion

and migration after arterial ischemia/reperfusion (47, 191). Discovery of drugs to inhibit various elements of the proinflammatory cascade induced by disturbed flow, particularly the WBC-EC interactions that are important in many aspects of the disease, may offer the greatest opportunity to prevent chronic venous diseaserelated complications (163). Improved understanding of the molecular and cellular mechanisms involved in disturbed flow-mediated pathogenesis of chronic venous diseases can lead to the identification of new molecular targets for pharmacologic intervention.

IX. SUMMARY AND CONCLUSIONS

The EC monolayer, located at the interface between the flowing blood and the vessel wall, is directly exposed to blood flow and associated shear stress, and its dysfunction in response to chemical and mechanical stimuli can lead to vascular disease. Disturbed blood flow patterns (e.g., flow separation, recirculation, reattachment, stasis, and reflux) occur naturally at certain vascular regions (such as arterial branch points and curvatures) and the aortic and venous valve sinuses, as well as in pathophysiological conditions (such as atherosclerotic plaques, incompetence of venous valves and outflow obstruction, etc.) and following interventional procedures (such as end-to-side anastomosis in bypass graft surgery and stent deployment in balloon angioplasty). The flow disturbances that occurred naturally or associated with vascular diseases and interventions can lead to neointimal hyperplasia or thrombosis, which result in undesirable vascular consequences and clinical conditions, including atherosclerosis, restenosis following angioplasty, in-stent restenosis, bypass graft occlusion, transplant vasculopathy, and aortic valve calcification, as well as various chronic venous diseases. In this review, we have summarized the current state of in vitro and in vivo research on the effects of disturbed flow and the associated alterations in shear stress on ECs, in terms of signal transduction, gene expression, and cellular structure and functions (for summary, see Figs. 22 and 23). In the relatively straight portion of an artery, which is exposed to laminar flow with a physiological level of shear stress (10–70 dyn/cm^2), ECs are aligned and elongated in the direction of flow, with the formation of very long, well-organized, parallel actin stress fibers in the central region and the continuous distributions of intercellular junctional proteins (e.g., Cx43 and VE-cadherin) in the periphery. In contrast, in areas of disturbed flow, i.e., the arterial branch points and curvatures, the ECs are more polygonal in appearance without a clear orientation; their actin filaments are short, randomly oriented, and localized mainly at the cell periphery, and their intercellular junctional proteins have discontinuous distributions. The accelerated cell turnover rate at regions of disturbed flow probably plays a significant role in the disruption of junctional proteins and the consequent increase in permeability to macromolecules such as lipoproteins. In these regions, there is also a sustained activation of SREBP, which acts in concert with the increase in permeability to contribute to the increase in lipid accumulation in regions of disturbed flow.

Sustained laminar shear stress in a physiological range with a definitive net direction activates signaling pathways that induce the expression of several atheroprotective and antithrombogenic genes encoding products that serve antioxidant, anti-inflammatory, anticoagulant, and antiapoptotic functions. These protective effects of laminar shear stress are mediated via a number of mechanisms, including the inhibition of cytokine-induced EC signaling, suppression of EC proliferation, and modulation of SMC phenotype toward contractile. In contrast, disturbed flow with a low and reciprocating shear stress and a high shear stress gradient induces the expression of a number of atherogenic and thrombogenic genes (pro-oxidant, pro-inflammatory, pro-coagulant, and pro-apoptotic), enhancement of EC proliferation, and modulation of SMC phenotype toward synthetic. These findings indicate that laminar shear stress in a physiological range maintains vascular homeostasis and plays protective roles against atherosclerosis and thrombosis, whereas EC dysfunction

induced by disturbed flow with low and reciprocating shear stress would predispose these vascular regions to atherogenesis and thrombosis.

Disturbed flow may also occur in the aortic and venous valve sinuses, which may lead to the sideness of valvular endothelial phenotypes and responses that contribute to the side-specific susceptibility to calcification or thrombosis. The response of valvular ECs to shear stress may be different from that of vascular ECs, in terms of gene expression and structure. In contrast to parallel alignment of vascular ECs exposed to unidirectional laminar flow, the aotic valvular ECs tend to be perpendicularly oriented to the direction of flow. The transcriptional profile of the endothelium on the aortic side of aortic valvular leaflets is different from that on the ventricular side, with higher expression of proinflammatory factors and lower expression of calcification inhibitors, suggesting the side-specific permissiveness to atherosclerosis and calcification. The sideness of venous valvular endothelium is evidenced by the finding that venous valvular sinus endothelium maintains a thromboresistant phenotype, with higher expression of anticoagulant and anti-inflammatory factors compared with the endothelium on the opposite side of valvular leaflets, which may play homeostatic roles in protecting against venous thrombogenesis.

The responses of venous ECs to disturbed flow resulting from reflux through incompetent valves and outflow obstruction or stasis in patients with chronic venous diseases resemble the responses of arterial ECs in atherogenesis, in terms of increased adhesion and transmigration of WBCs and elevated expressions of adhesion molecules ICAM-1, VCAM-1, and E-selectin, proteases MMP-2 and MMP-9, and mitogens VEGF and PDGF, and production of ROS at the vein wall or release into the plasma. These responses of venous ECs to disturbed flow render the veins more susceptible to inflammation, leading to the development and progression of various chronic venous diseases, including varicose veins, deep venous thrombosis, and chronic venous insufficiency. There are differences for ECs from veins and arteries. For example, venous ECs may have greater capacity to mount an inflammatory response compared with arterial ECs, and this may influence the development of venous thrombosis and vein graft atherosclerosis in which the inflammatory responses play major roles. Identification of specific biomarkers and mechanisms accounting for the endothelial heterogeneity between arteries and veins and among different vascular beds, as well as the role of this heterogeneity in the pathophysiology of vascular diseases, may provide novel approaches for site-specific therapeutic intervention for cardiovascular diseases.

Vascular biology has emerged as an important discipline in basic biomedical sciences and clinical medicine, and there is increasing recognition of the necessity of considering both mechanical and chemical factors in vascular biology in health and disease. Studies on the effects of disturbed flow on ECs have produced important information on the interplays between blood flow and vessel geometry in the development of intimal hyperplasia, atherosclerosis, thrombosis, chronic venous diseases, and their clinical complications. The application of such information to clinical medicine and surgery has emerged only recently. One example of the application is the design and improvement of reconstructive procedures that take into account the flow mechanics to optimize their success in vascular surgery. For example, the mechanical compliance and geometry of graft-to-artery distal anastomoses in bypass vascular surgery play significant roles in determining early and late graft successes/failures due to thrombosis, neointimal hyperplasia, and atherosclerosis; optimization of the factors considered in this review can significantly improve the outcome. Furthermore, investigations on EC responses to disturbed flow will provide important information concerning alterations in vascular signaling, gene expression, and function in the disease-prone regions. These results can help to develop new methods to distinguish the dysfunctional or activated ECs from healthy or quiescent ECs. Elucidation of the dynamic

interactions between disturbed flow-induced EC dysfunction and systemic risk factors, such as smoking, hyperlipidemia, hyperglycemia, hypertension, obesity, and diabetes, will enhance our understanding of the pathophysiological mechanisms of vascular diseases, thus improving the success of therapeutic modalities used to counter disease progression and improve clinical outcomes. A major challenge in this field is to conduct innovative, interdisciplinary research that combines bioengineering, physiology, other biomedical sciences, and clinical medicine to elucidate the role of disturbed flow in the pathophysiology of cardiovascular diseases, with the ultimate goal of integrating and translating the large body of information for the development of novel therapeutic strategies for these diseases.

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GLOSSARY

Complex flow patterns	The patterns of flow that are difficult to characterize; they can be made of many different types of flow such as disturbed flow, reciprocating flow, recirculation eddy, flow separation and reattachment, etc.
Cyclic stretch	Periodic lengthening of elements in the vessel wall in the circumferential direction produced by periodic increases in transmural pressure difference, or periodic lengthening of the cultured endothelial cells in one direction (uniaxial cyclic stretch) or all directions (biaxial cyclic stretch).
Disturbed flow	The pattern of flow that is nonuniform and irregular, including recirculation eddies and changes in direction with time (reciprocating flow) and space (flow separation and reattachment).
Flow reattachment	After flow separation, the part of the flow that forms the boundary between the recirculating flow and the forward flow through the central region of the tube (vessel) is called the dividing streamline. The point at which the dividing streamline attaches to the wall again is called the flow reattachment point, where the velocity gradient and shear stress vanish to become zero.
Flow separation	The boundary layers of flow that separate from the surface of the vessel wall to form a recirculation eddy behind the separation point, where the velocity gradient and shear stress vanish.
Fluid shear stress	The tangential component of frictional forces generated at a surface (e.g., the vessel wall) by the flow of a viscous fluid (e.g., blood). The unit for shear stress is Pascal (Pa) in the SI system (the International System of Units). In the cardiovascular system, dyn/cm^2 is usually

	used: 1 Pa = 10 dyn/cm^2. The “shear stress” used in this article denotes wall shear stress unless otherwise stated.
Hydrostatic pressure	The pressure exerted by a fluid at equilibrium due to the force of gravity.
Laminar flow	A well-ordered pattern of streamlined flow that occurs when a fluid flows in parallel layers, with friction between the successive layers.
Pulsatile flow	Periodic flow with a positive mean flow rate; the velocity of the fluid oscillates in time at the frequency of the periodicity with a significant net direction.
Reciprocating flow	Periodic flow with little mean flow rate; the velocity of the fluid oscillates in time mainly back and forth at the frequency of the periodicity.
Recirculation eddy	Swirling of a fluid with reverse streamlines created when the fluid flows past an obstacle, a curvature, or a region with diameter change.
Reflux	The reflux in the venous system is defined as a pathophysiological retrograde (distally directed) flow in an incompetent vein that occurs between the veins in the thigh and the lower leg of an individual in an erect position and under the influence of gravitation.
Retrograde flow	The flow of fluid in a direction other than the physiological direction, as in reflux.
Step flow	The flow over a backward-facing step, which is achieved in the cone-and-plate viscometer by imposing a rectangular obstacle or in the parallel-plate flow chamber by using two silicone gaskets with the top one having a longer longitudinal cutout than the one below (Fig. 8). This flow is comprised of a well-defined recirculation eddy immediately downstream of the step, followed by a region of flow reattachment, and finally with a unidirectional laminar flow that is reestablished further downstream (Fig. 9).
Turbulent flow	Flow in which the velocity at any given point varies continuously over time, even though the overall flow may be steady. In turbulent flow, the inertial forces are more significant than viscous forces; it begins to be significant when the Reynolds number (flow velocity × fluid density × vessel diameter/fluid viscosity) exceeds a critical level; this critical Reynolds number becomes lower with an increase in complexity of vascular geometry. Turbulent blood flow is uncommon in normal circulation, but it occurs in human aorta at peak systole (especially during heavy exercise), in arteries distal to severe stenoses, and in aneurysms.

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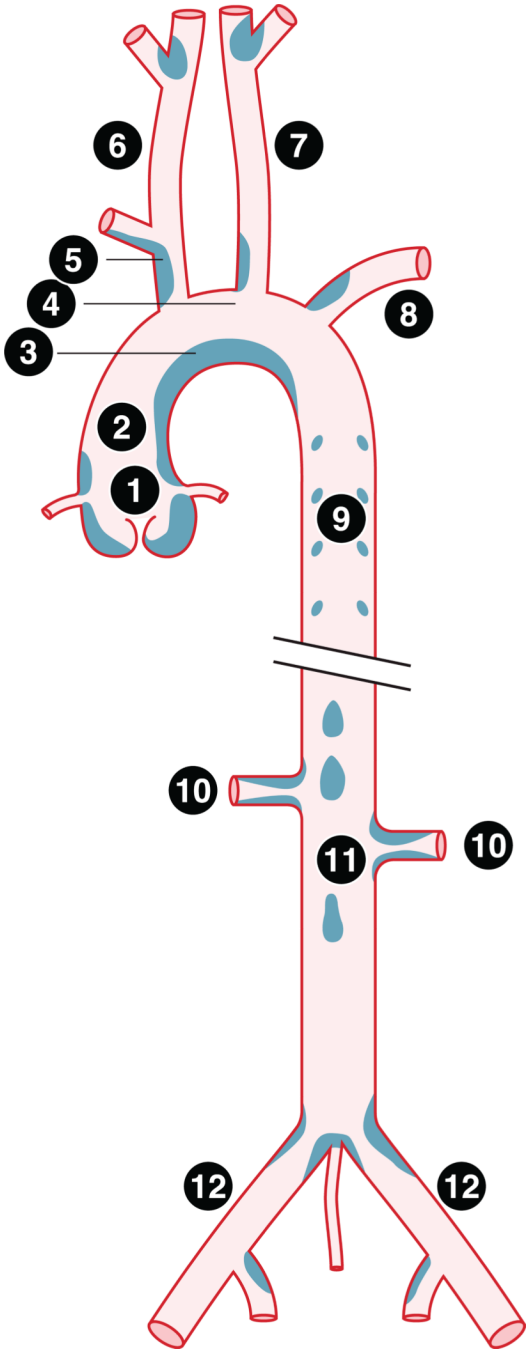


FIG. 1.

Atherosclerosis preferentially develops at arterial branches and curvatures. Schematic drawing shows a longitudinal representation of the major arterial vasculature illustrating the observed distribution of atherosclerotic plaques (gray shading) in the vasculatures of $LDLR^{-/-}$ mice fed a high-fat atherogenic diet. *1*, Aortic sinus; *2*, ascending aorta; *3*, inner (lesser) curvature of aortic arch; *4*, outer (greater) curvature of aortic arch; *5*, innominate artery; *6*, right common carotid artery; *7*, left common carotid artery; *8*, left subclavian artery; *9*, thoracic aorta; *10*, renal artery; *11*, abdominal aorta; *12*, iliac artery. [Redrawn from VanderLaan et al. (590).]

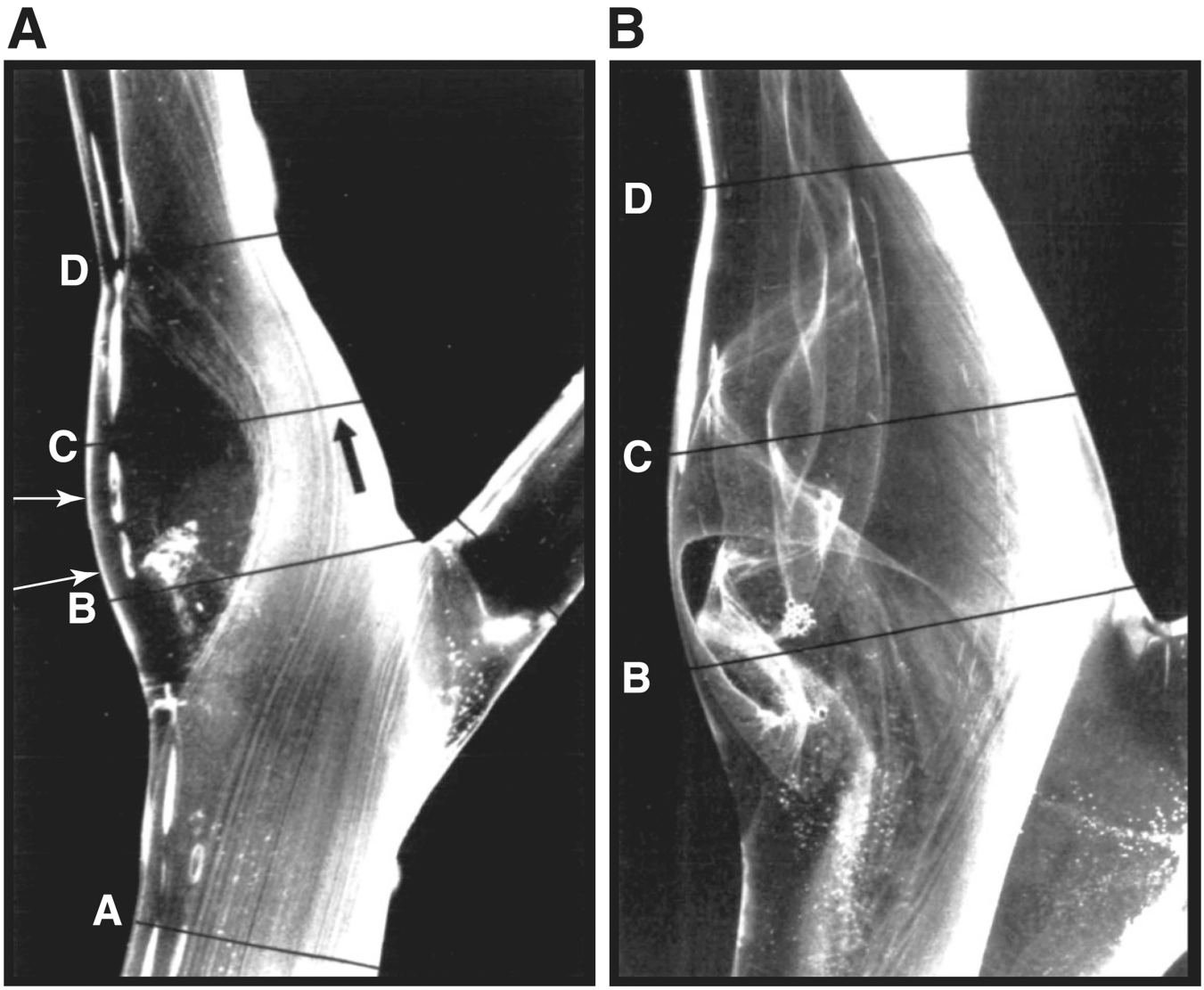


FIG. 2.

Hydrogen bubble visualization of flow in molds of carotid bifurcation. Flow visualizations were made with flow division ratio between internal and external carotid branches of 70:30 and Reynolds number (based on the inlet flow rate and hydraulic diameter) of 400 (*A*) and flow division ratio of 80:20 and Reynolds number of 800 (*B*) to show the effects of these hemodynamic parameters on flow pattern. *A*: flow is rapid, laminar, and longitudinal along the common carotid artery and the inner wall of the internal carotid sinus (black arrow); a large area of flow separation is formed along the outer wall of the sinus (white arrows). *B*: streamlines are skewed towards the apex of the bifurcation, and complex helical flow patterns occupy the separated flow region of the sinus. The five areas indicated are as follows: *A*, common carotid; *B*, proximal internal carotid; *C*, midpoint of carotid sinus; *D*, distal internal carotid; *E*, external carotid. [From Zarins et al. (644).]

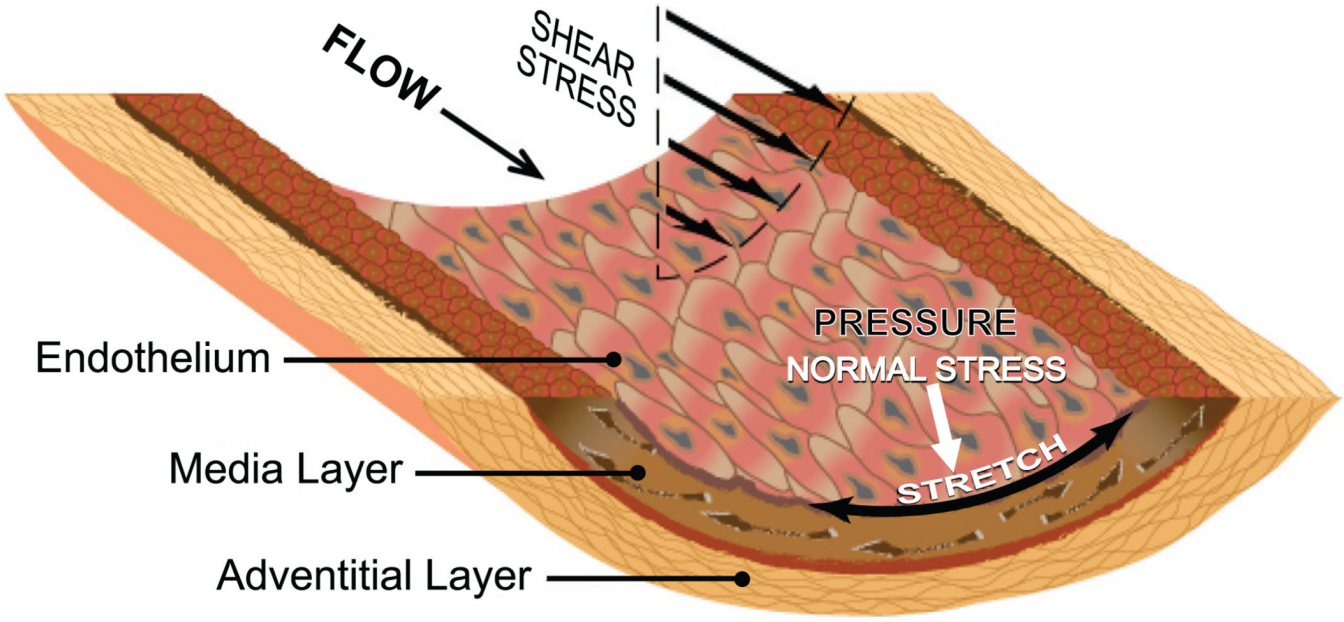


FIG. 3.

Schematic diagram showing the generation of shear stress (parallel to the endothelial cell surface) by blood flow and the generation of normal stress (perpendicular to the endothelial cell surface) and circumferential stretch due to the action of pressure. (Shu Chien and Yi-Shuan Li, unpublished Figure.)

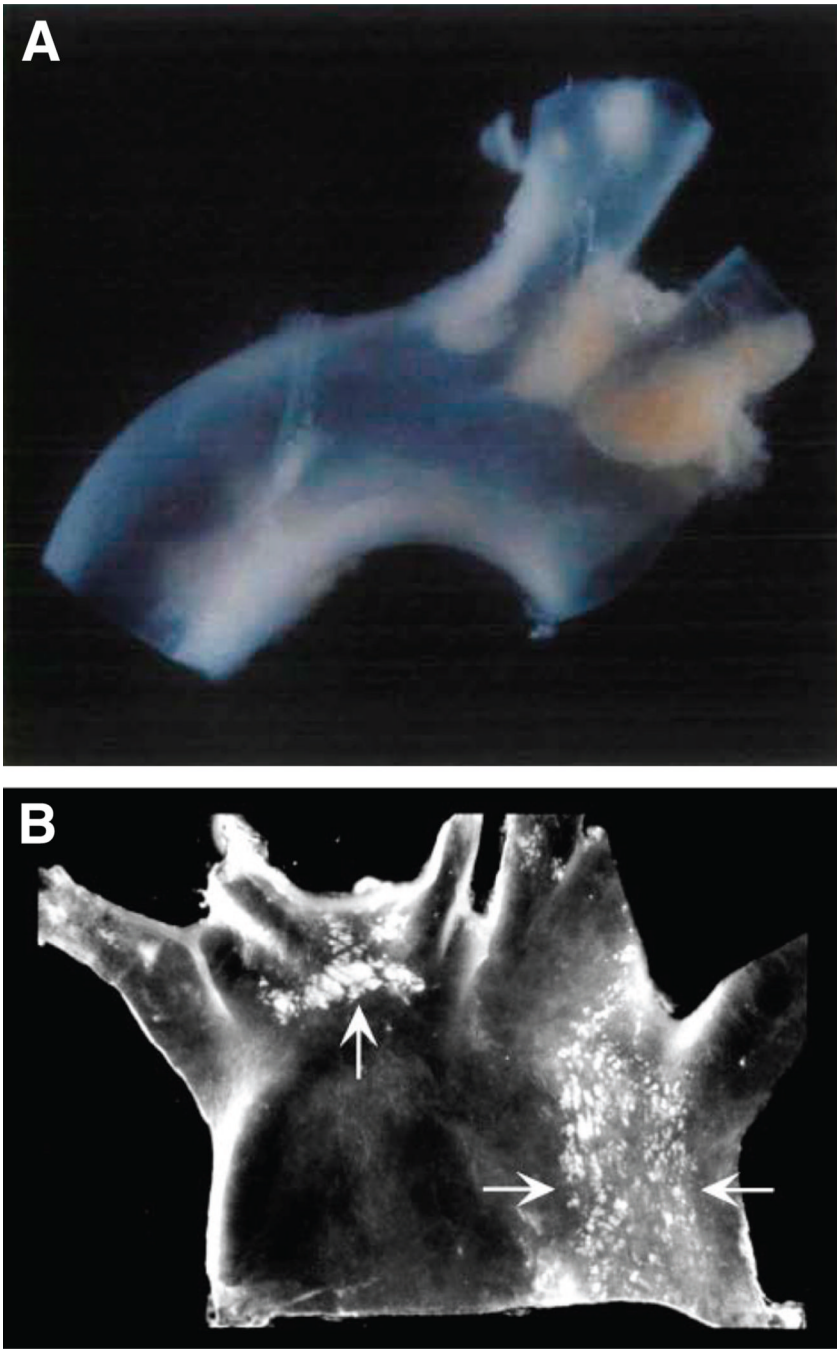


FIG. 4.

Atherosclerotic lesions in the aortic arch. *A*: gross appearance of atherosclerotic lesions in the aortic arch of a 20-wk-old ApoE$^{-/-}$ mouse fed the chow diet. Yellowish-white lesions are observed in regions of inner curvarure of the aortic arch and at the orifices of the arch branches. The more yellowish material in the branches is adventitial fat tissue. *B*: thin and transparent aorta of mouse allows direct visualization of early lesions in ApoE$^{-/-}$ mice by dissection microscopy. Under reflected light, elevated white lesions are visible on the luminal surface of the aortic arch of a 8-wk-old ApoE$^{-/-}$ mouse fed the Western-type diet. Two areas of lesion development are prominent and contain opaque sites of lesion

formation: the lesser curvature (on the *right*, between the arrows) and the orifice of the arch branches (on the *left*, single arrow). [From Nakashima et al. (406, 407).]

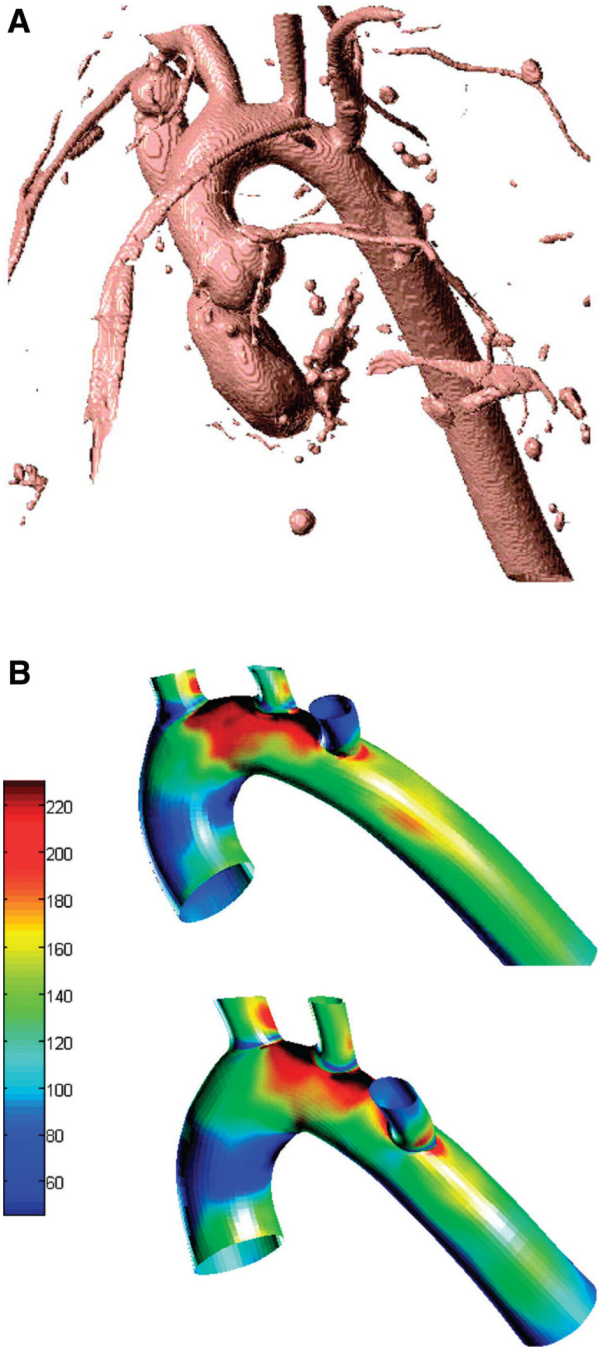


FIG. 5.

Shear stress distributions in mouse aortas. *A*: a representative image of mouse aortas illustrated by micro-CT scan. For reference, the diameter of the descending aorta is ~1 mm. *B*: distributions of mean shear stress in the aortas. Velocities in the aortas are measured by Doppler ultrasound. Mean values of wall shear stress are computed by averaging wall shear stress magnitudes over the cardiac cycle. Colors are used for scaling the values in dyn/cm^2, and data are shown for two different mice. The mean wall shear stress in the mouse is much higher than that in the human (553), although the inner curvature of the arch and the entrance to the orifice of the innominate artery are areas of lower shear stresses. On the other

hand, lateral surfaces of the ascending aorta and the region of the arch around the branch of left common carotid artery experience higher shear stress values. [From Suo et al. (552).]

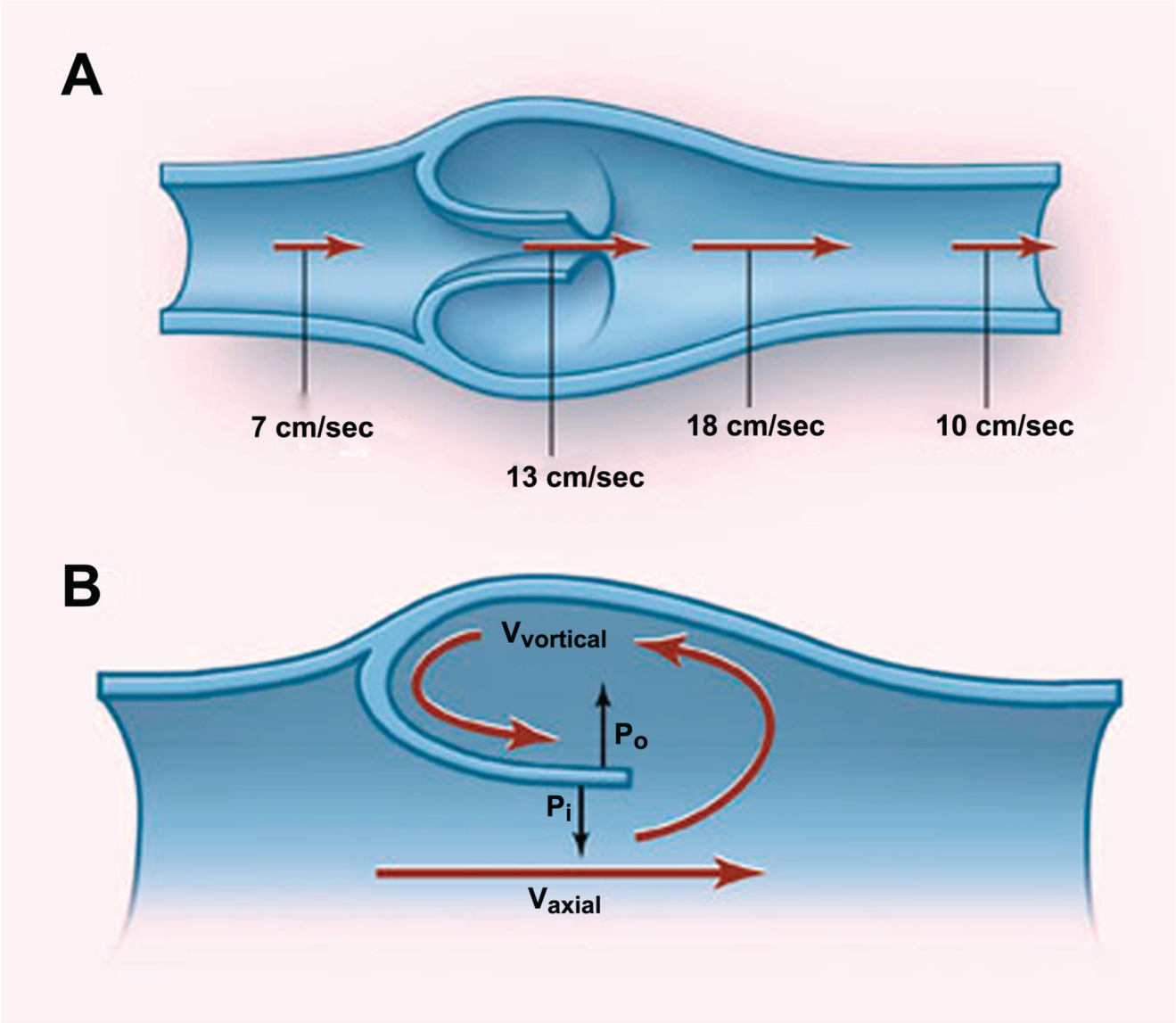


FIG. 6.

Velocity of blood flow through a venous valve and forces acting on a venous valvular leaflet. *A*: the reduced cross-sectional area between the valvular leaflets produces a proximally directed jet of increased axial velocity. *B*: axial flow between the leaflets generates a pressure (P_o) that tends to keep the leaflet in the open position, and vortical flow in the valve pocket generates a pressure (P_i) that tends to close the leaflet. These pressures depend on the respective flow velocities ($V_{vortical}$ and V_{axial}); pressure is inversely related to velocity. [From Bergan et al. (36).]

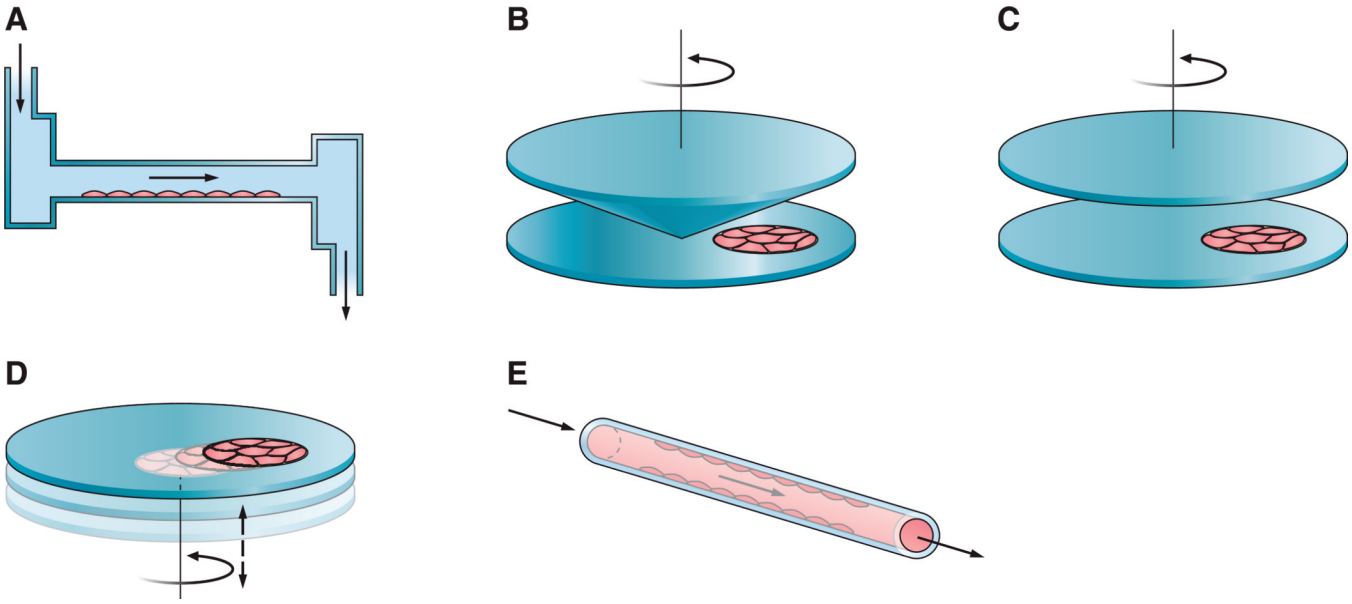


FIG. 7.

The configutrations for in vitro systems for applying shear flow to ECs. *A*: parallel-plate flow chamber. *B*: cone-and-plate viscometer. *C*: parallel disk viscometer. *D*: orbital shaker. *E*: tubular or rectangular capillary tube. It is noted that, for ease of visualization, the ECs are not drawn all around the inner lumen of the tube.

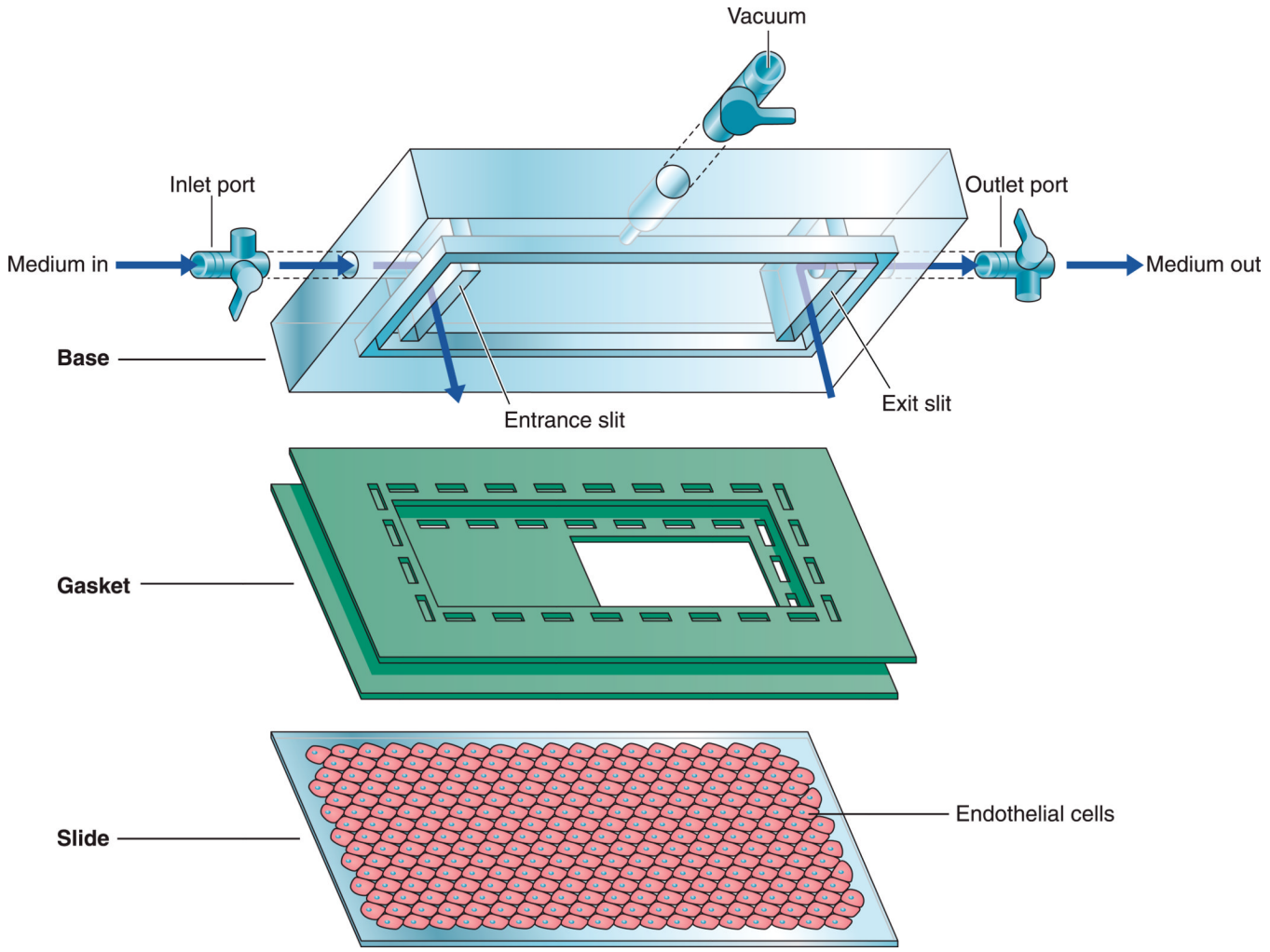


FIG. 8.

Diagram showing the parallel-plate flow chamber for vertical-step flow. The polycarbonate base plate (*top*), two gaskets with different open areas, and the glass slide with EC monolayer (*bottom*) are held together by a vacuum suction applied at the perimeter of the slide, forming a channel with a lesser depth at the entrance, creating a step. Cultured medium enters at inlet port through entrance slit into the channel and exits through exit slit and outlet port.

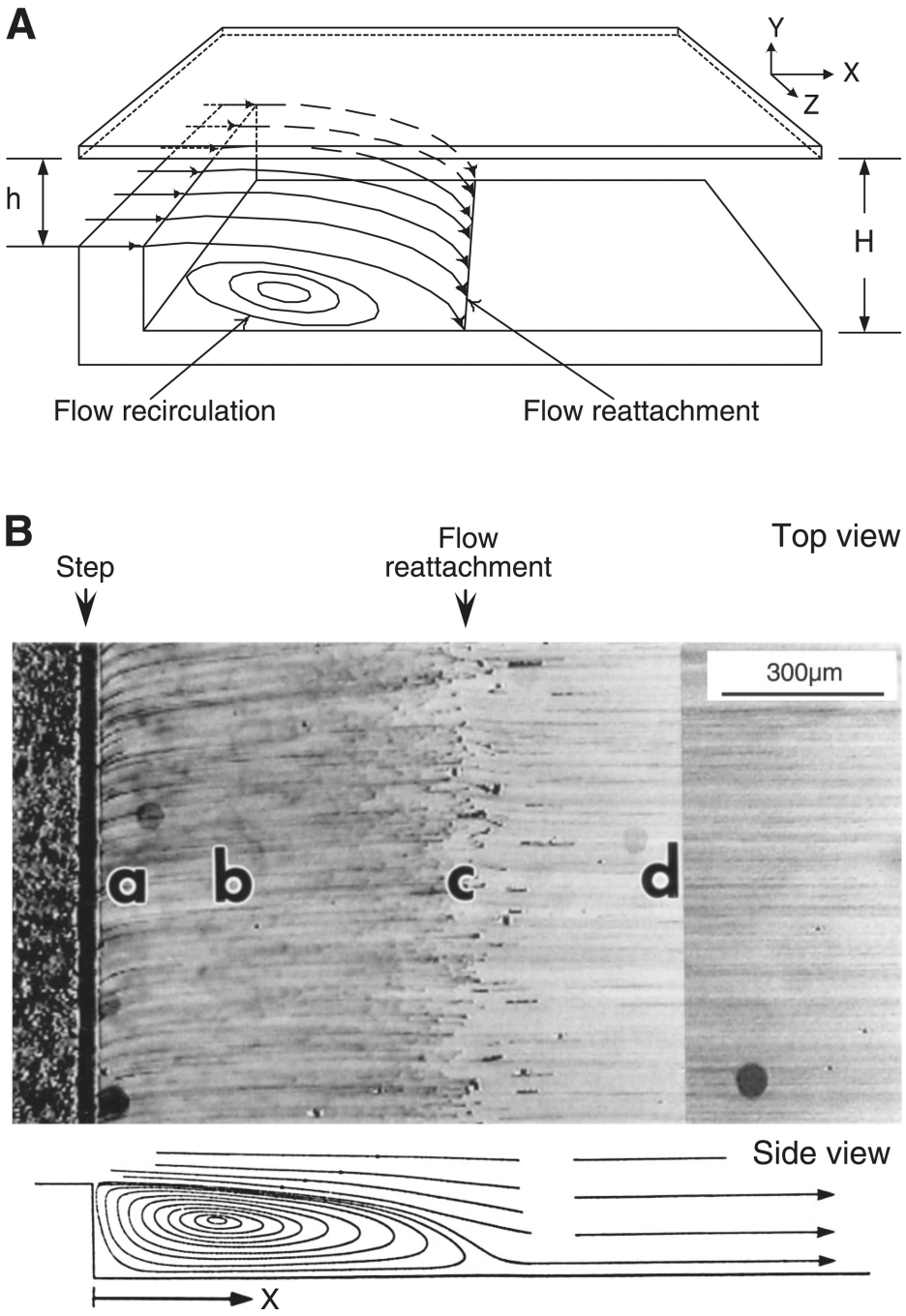


FIG. 9.

Visualization of flow patterns created in vertical-step flow channel. *A*: schematic diagram of the flow channel showing the flow pattern immediately beyond the step. *h* and *H* are heights of the channel above the step and beyond the step, respectively. *B, top*: phase-contrast photomicrograph (top view) of experimental flow patterns in the vertical-step flow channel. Flow is from *left* to *right* and is made visible with marker microparticles (1 μm in diameter). Flow separation occurs in the region distal to the step, forming four specific flow areas: *a*, the stagnant flow area; *b*, the center of the recirculation eddy; *c*, the reattachment flow area; and *d*, the fully developed flow area. From on-line microscopic observations, the particles transported from the bulk flow along the curved streamlines with decreasing velocities

towards the wall near the reattachment point (area *c*). While some of the particles moved forward to rejoin the mainstream with increasing velocities, others moved in a retrograde direction towards the step as recirculation eddies. These latter particles moved upstream initially with increasing velocities and decelerated when approaching the wall of the step (area *a*), from where the particles were carried away from the floor of the chamber by upward curved streamlines. *Bottom*: schematic drawing of the side view of the streamlines in the vertical-step flow channel deduced from the top view photograph. [From Chiu et al. (88).]

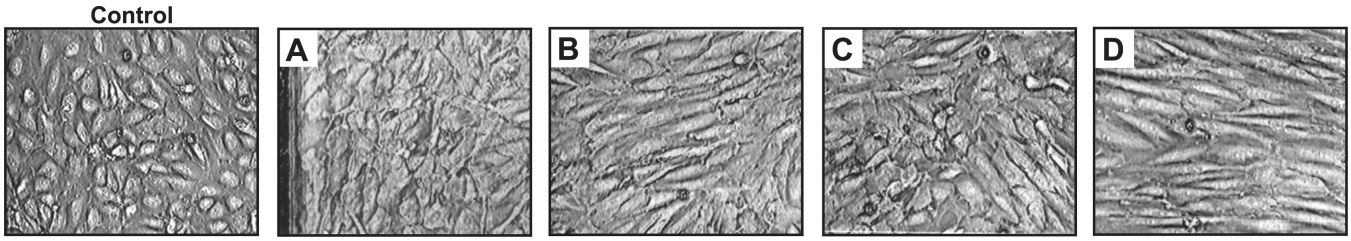


FIG. 10.

Morphological changes induced in a confluent EC monolayer by exposure to disturbed flow in the step flow channel. *A*, The stagnant flow area; *B*, the center of the recirculation eddy; *C*, the reattachment flow area; *D*, the fully developed flow area (same designations as in Fig. 9). The mean values of wall shear stress created in areas *A*, *B*, *C*, and *D* are characterized to be 0.5, 20, 0, and 20 dyn/cm^2, respectively, by measurements using micron-resolution particle image velocimetry (μPIV) and by computational simulation (88, 94). The direction of the main flow is *left* to *right*. Control photograph is from the same experimental monolayer before shearing (0 h). [Modified from Chiu et al. (94).]

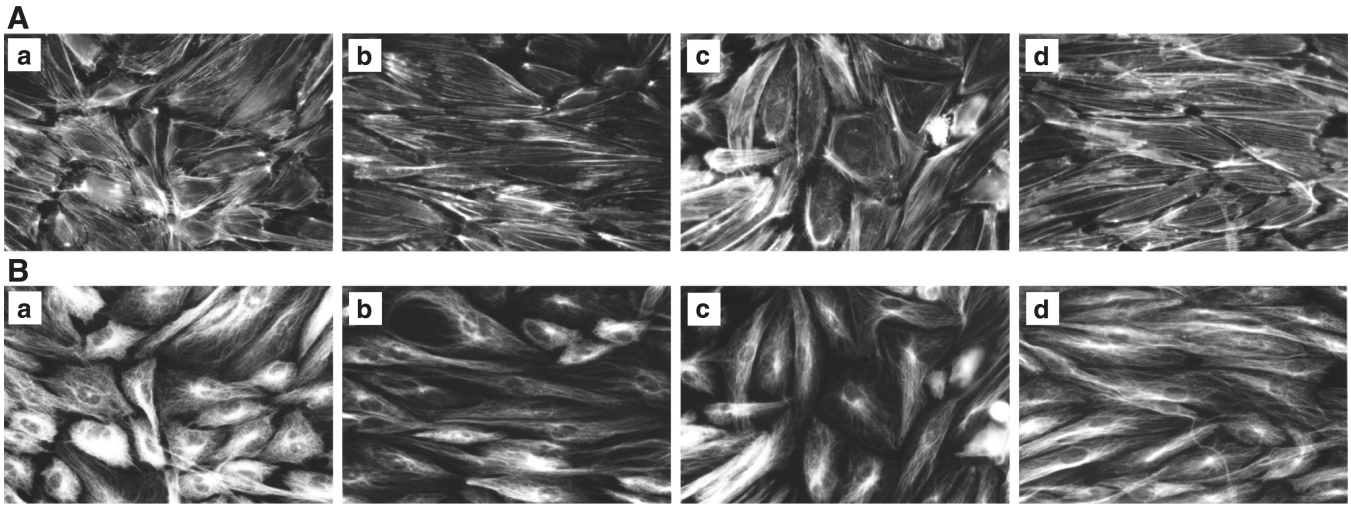


FIG. 11.

Fluorescence photographs of F-actin filaments (*A*) and microtubules (*B*) after exposure to disturbed flow in the step-flow channel for 24 h. *a*, The stagnant flow area; *b*, the center of the recirculation eddy; *c*, the reattachment flow area; *d*, the fully developed flow area (same designations as in Figs. 9 and 10). The direction of the main flow is *left* to *right*. Magnification: ×400. [Modified from Chiu et al. (94).]

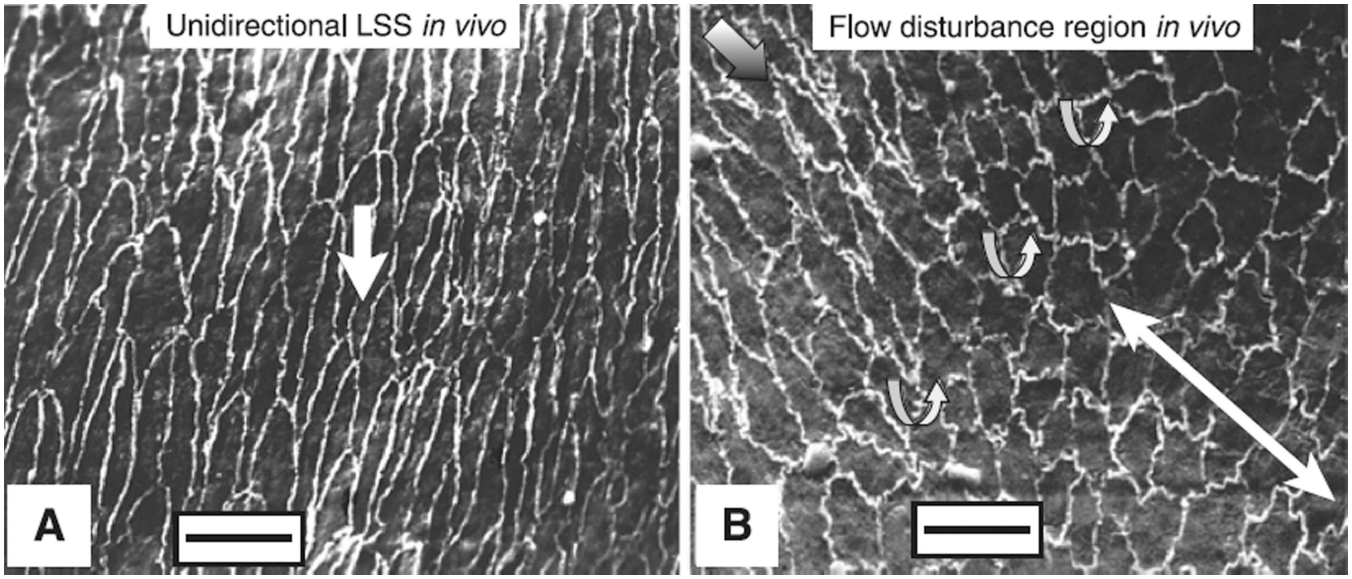


FIG. 12.

In situ observation of EC morphologies in regions of laminar and disturbed flows. *A*: EC alignment in unidirectional laminar flow in the descending thoracic aorta. The direction of flow is indicated by the downward white arrow near the center of the picture. *B*: morphological changes in ECs in regions near a branch of the aorta. ECs change their morphologies from aligned elongations to polygonal shape beyond a line of flow separation (curved arrows) that marks the boundary of a disturbed flow region where oscillating, multidirectional flow typically occurs (double-headed arrow). Scale bar in each panel = 15 μm. For details, see Davies (125). [From Davies (125).]

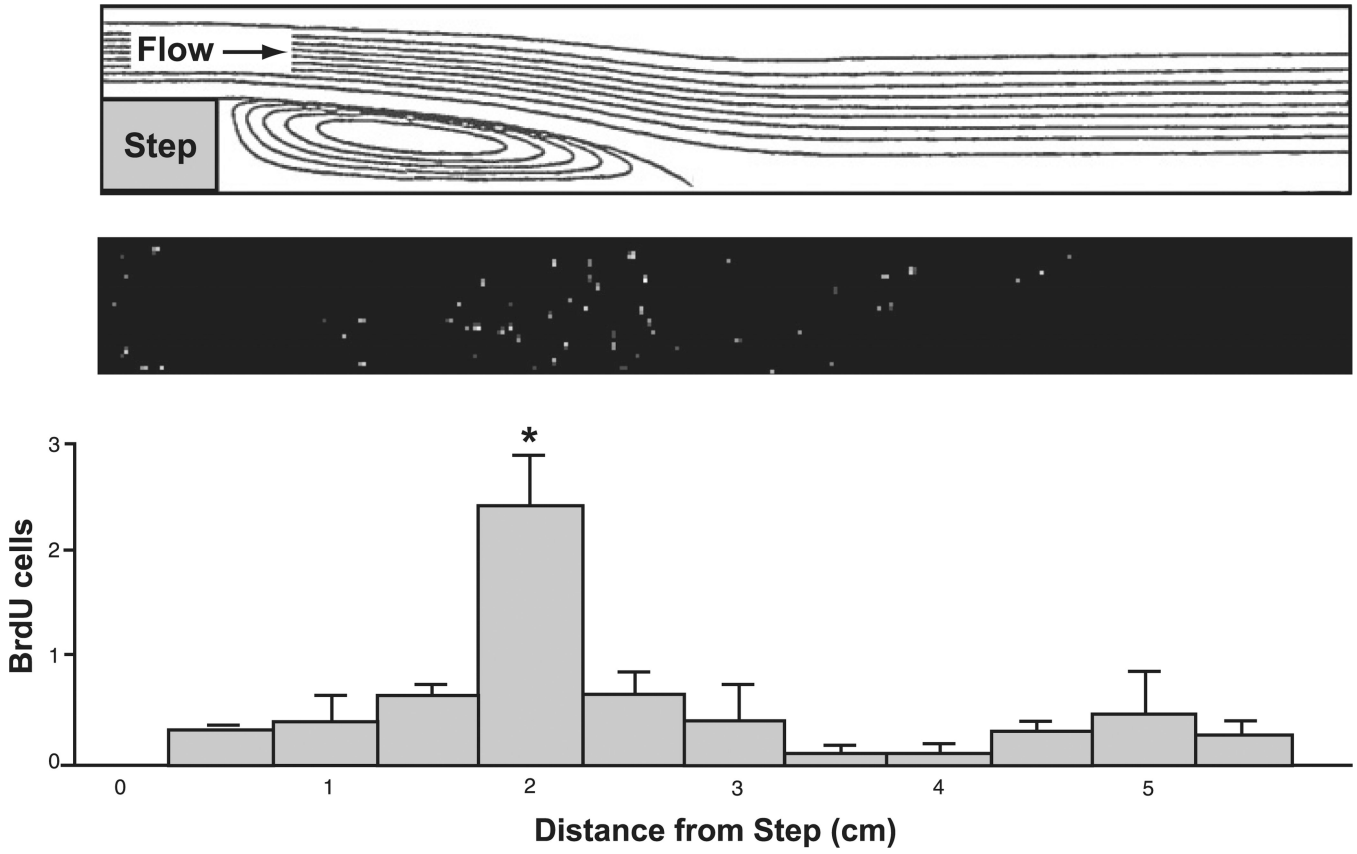


FIG. 13.

EC proliferative rate is increased in regions of disturbed flow. The proliferation of cultured bovine aortic ECs, as assessed by the BrdU incorporation assay, is markedly elevated in the disturbed flow region near the reattachment point in the step-flow channel. *Top panel* shows the side view of the step flow channel. *Middle panel* shows BrdU incorporation into ECs in one experiment. *Bottom panel* shows the BrdU incorporation into the ECs in four experiments. Bars are means ± SE. Asterisk indicates significant difference in BrdU incorporation in the region of disturbed flow near the reattachment point. Not shown in the bar graph is an increase in BrdU incorporation immediately next to the step. [From Chien (86).]

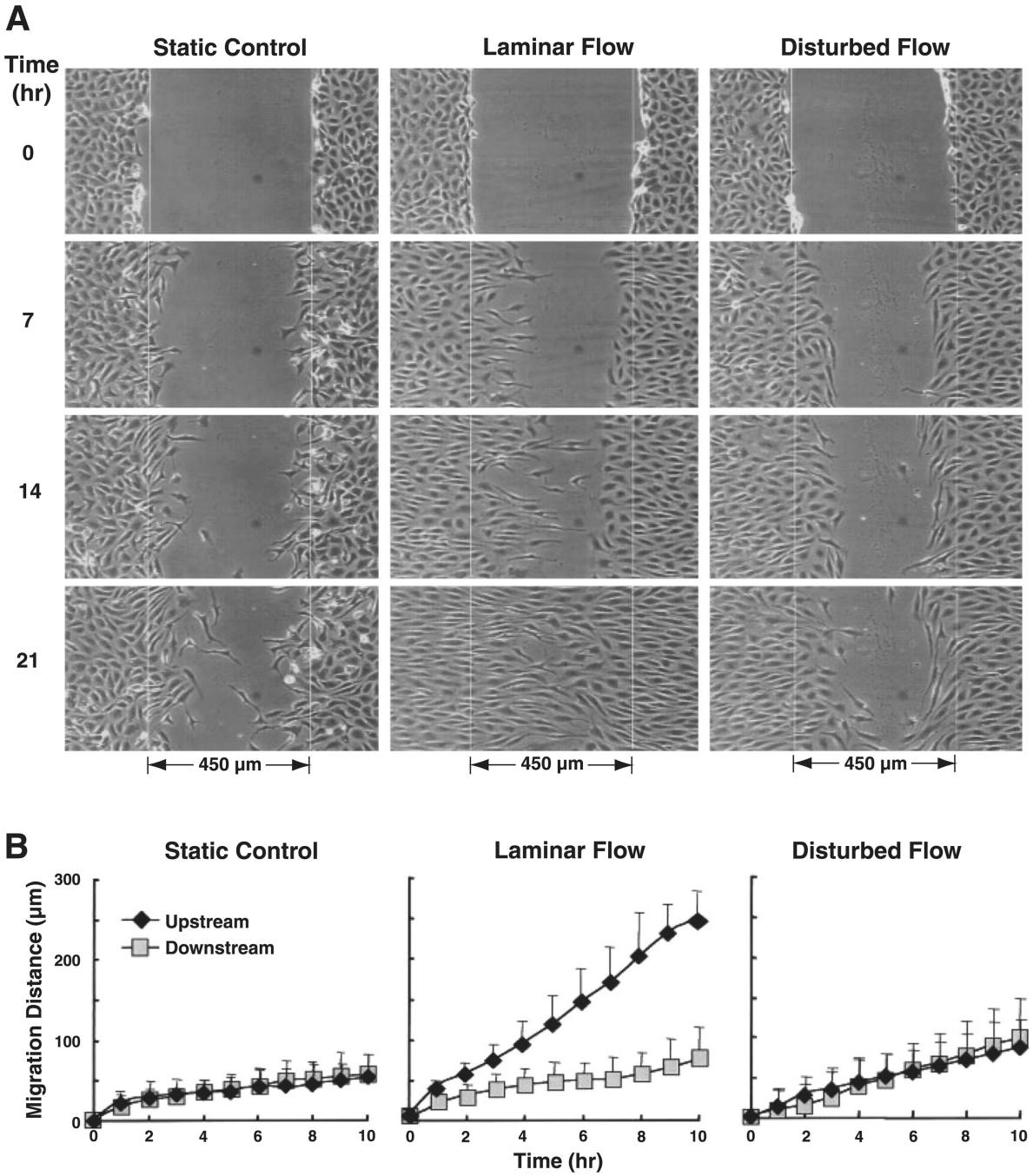


FIG. 14.

Laminar flow promotes EC migration compared with disturbed flow and static control. The wounded EC monolayers are kept under static conditions or are subjected to laminar or disturbed flow in a stepflow channel. The direction of laminar flow is from *left* to *right*. The left-hand side of the zone is denoted as "upstream" side, and the right-hand side is "downstream." *A*: phasecontrast images of the EC migration over the 21-h period of time. White vertical lines indicate the locations of wound edges at the beginning of the experiment. *B*: the net migration distance as a function of time for the cells in the first row at wound edges (both upstream and downstream sides). [From Hsu et al. (259).]

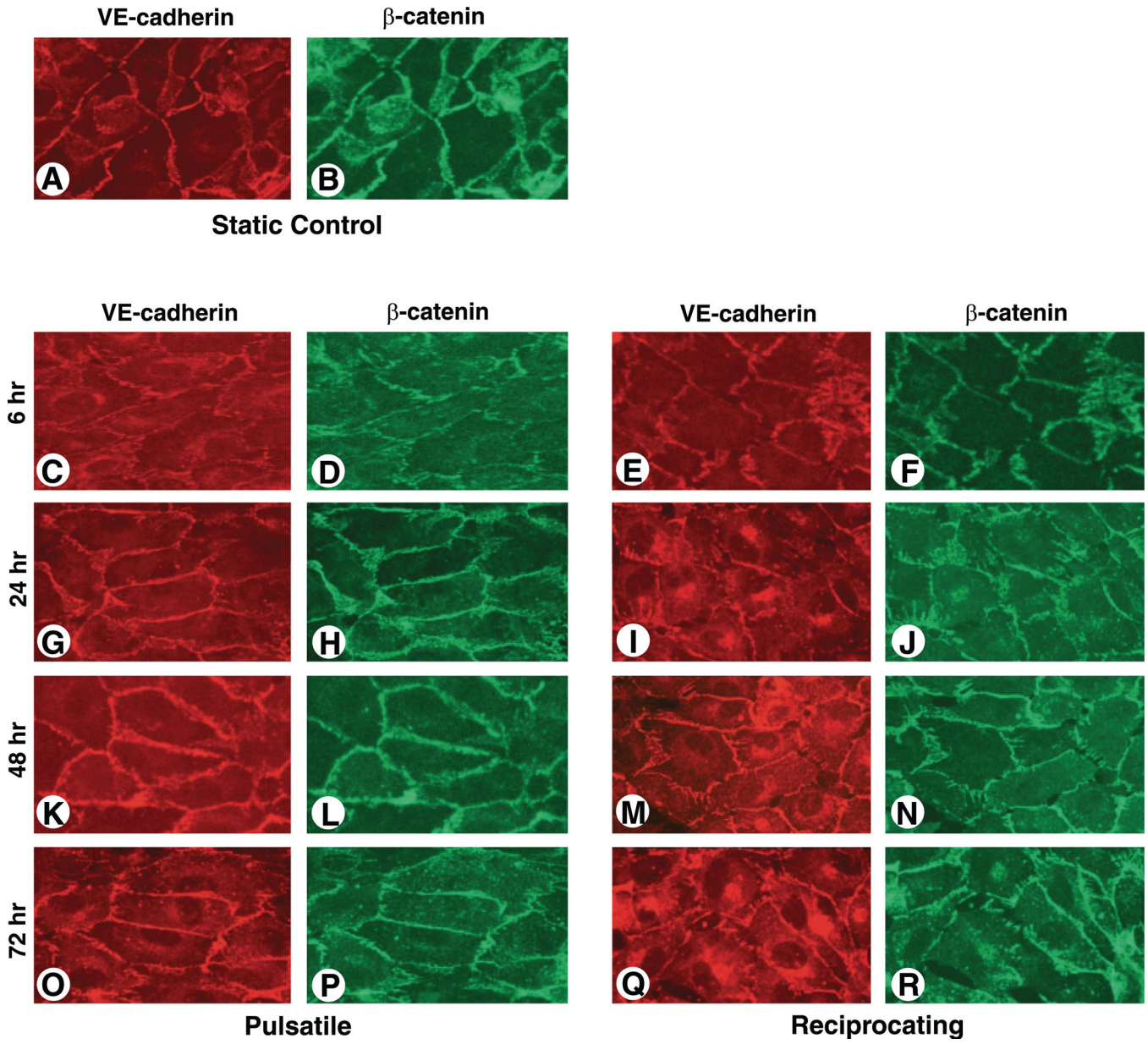


FIG. 15.

VE-cadherin and β-catenin staining in ECs exposed to pulsatile and reciprocating flows. Confluent monolayers of bovine aortic ECs are kept as controls (*A*, *B*) or subjected to different flow patterns in a flow chamber. VE-cadherin staining is observed by confocal microscopy. Stainings for VE-cadherin and β-catenin at intercellular junctions are discontinuous after exposing to pulsatile (*C*, *D*) or reciprocating (*E*, *F*) flow for 6 h. The distribution of these junction proteins becomes continuous around the entire periphery of the cells after 24, 48, or 72 h of exposure to pulsatile flow (*G*, *H*, *K*, *L*, *O*, *P*), but not reciprocating flow (*I*, *J*, *M*, *N*, *Q*, *R*). [From Miao et al. (379).]

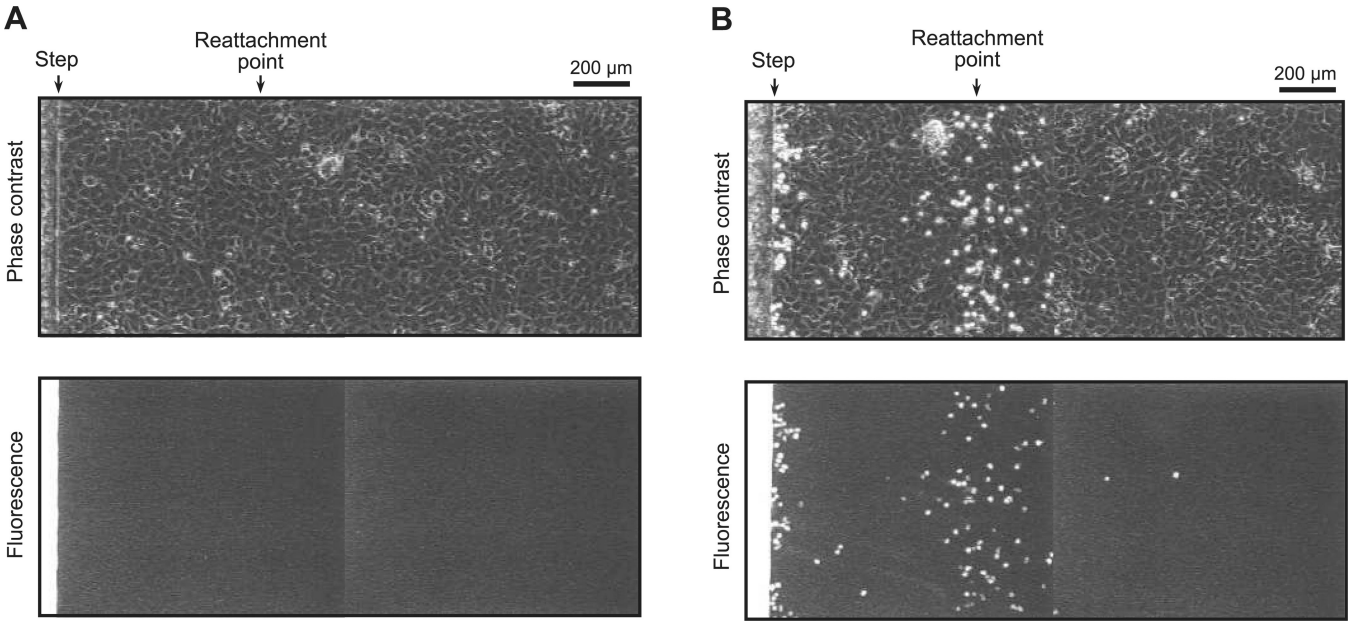


FIG. 16.

Enhancement of monocytic THP-1 cell adhesion to activated ECs by disturbed flow. ECs are maintained in static condition without (*A*) or with TNF-α (125 U/ml) treatment (*B*) for 4 h, and then exposed to disturbed flow in the step-flow channel with THP-1 cell suspension at a concentration of 5×10^5 cells/ml. Prior to the perfusion, THP-1 cells are labeled with calcein-AM at a concentration of 7.5 mM for 30 min to facilitate visualization of the cells under fluorescence optics against the endothelial background. Phase-contrast and corresponding fluorescent microphotographs are taken after 10 min of perfusion. [From Chiu et al. (88).]

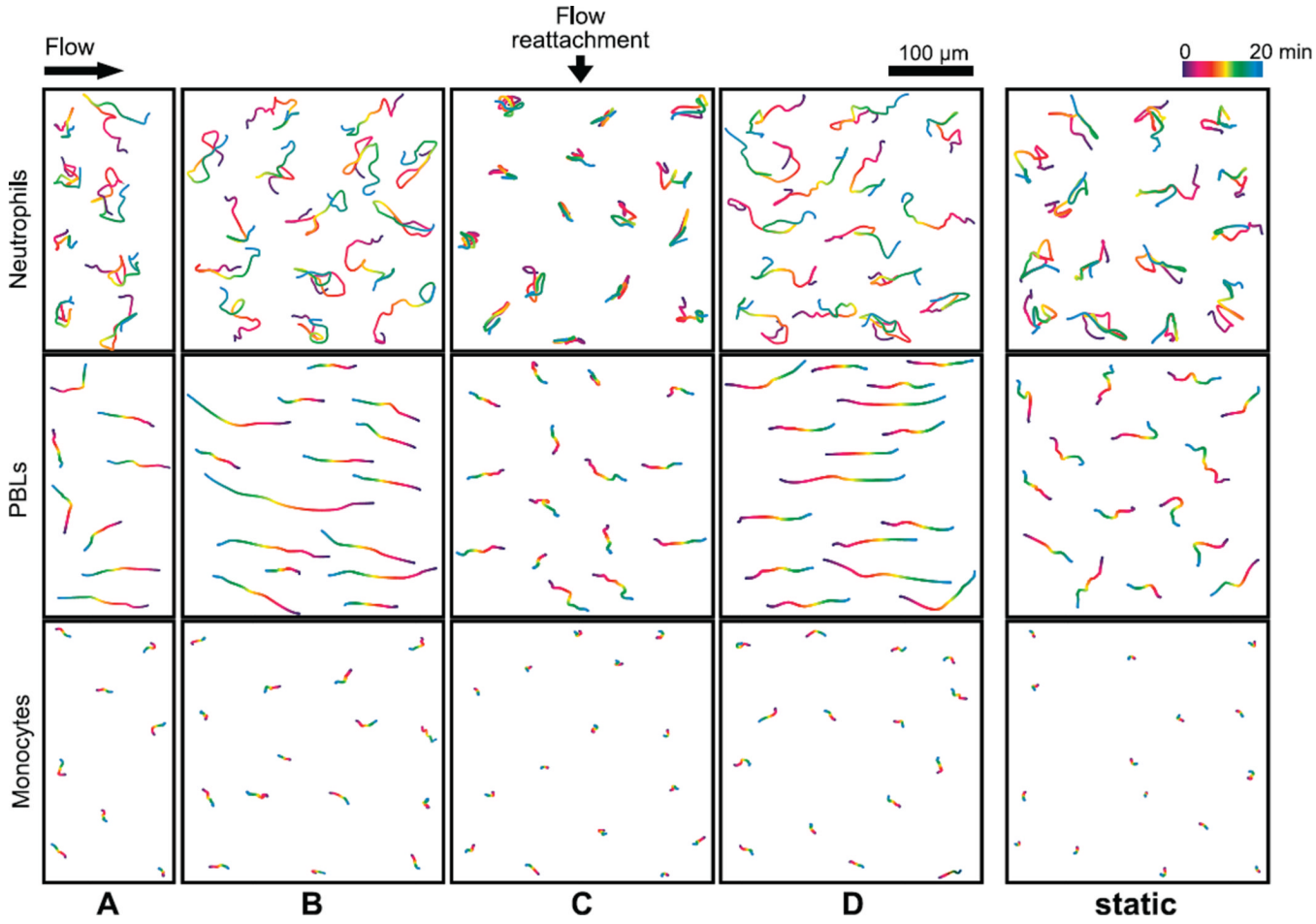


FIG. 17.

Neutrophils, peripheral blood lymphocytes, and monocytes show different migratory behaviors in EC/SMC coculture under disturbed flow. Purified neutrophils, peripheral blood lymphocytes (PBLs), and monocytes are perfused over the EC/SMC coculture in the step-flow channel, and the migration of arrested WBCs is traced for 20 min in areas *A*, *B*, *C*, and *D* (same designations as in Figs. 9–11) or under static condition after their transmigration across the EC monolayer to the underside. This figure shows the results of a representative experiment containing 8 cells migrating in area *A* and 15 cells migrating in areas *B*, *C*, and *D*, as well as under static condition. The positions of the centers of the cells are determined at 20-s intervals from 0 to 20 min, and their paths of travel are processed with a commercialized image analysis software. [From Chen et al. (76).]

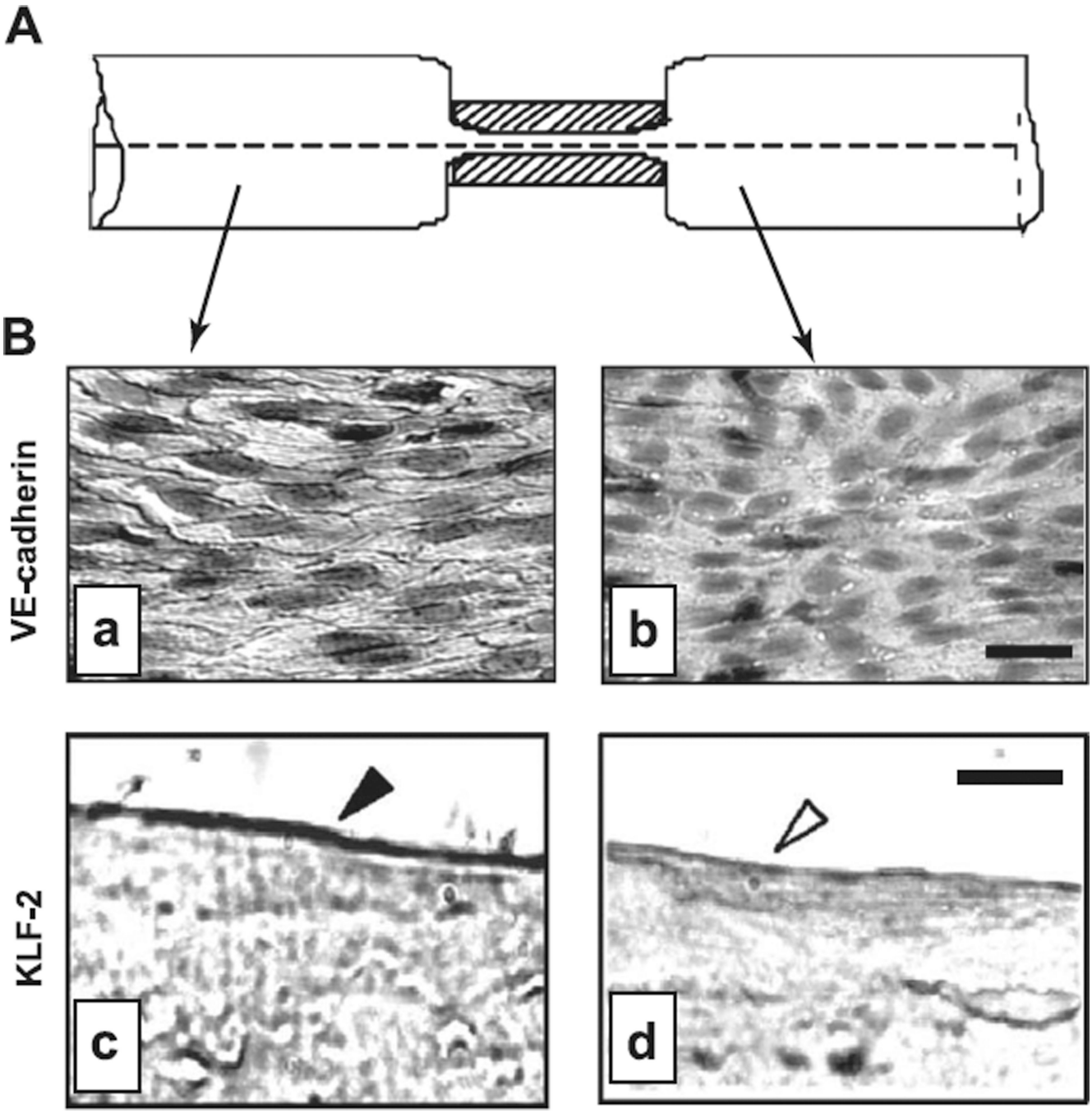


FIG. 18.

In vivo observations of VE-cadherin distribution and KLF-2 expression in response to disturbed versus laminar flows. *A*: side view of the rat abdominal aorta with a local stenosis created by using a U-shaped titanium clip, with the aim of studying the effects of flow patterns on VE-cadherin distribution and KLF-2 expression in vivo. Four weeks after the creation of stenosis, the vessel is harvested, fixed, embedded, sectioned longitudinally, and subjected to immunohistochemical staining with anti-VE-cadherin (*a* and *b*) or anti-KLF-2 (*c* and *d*) (*B*). Blood flow is from *left* to *right*, as indicated by the arrow. In the laminar flow region 5 mm upstream (as well as 5 mm downstream; not shown) to the clip site, VE-cadherin is highly expressed at EC borders (*B–a*), and the endothelium shows strong KLF-2

staining (closed arrowhead) (*B–c*). No detectable VE-cadherin is found at cell borders in the disturbed flow region downstream to the constriction (*B–b*). In this region, there is also a lack of KLF-2 staining (open arrowhead) (*B–d*). Bars in *B–b* and *B–d* are 30 and 10 μm, respectively. [From Miao et al. (379) and Wang et al. (600).]

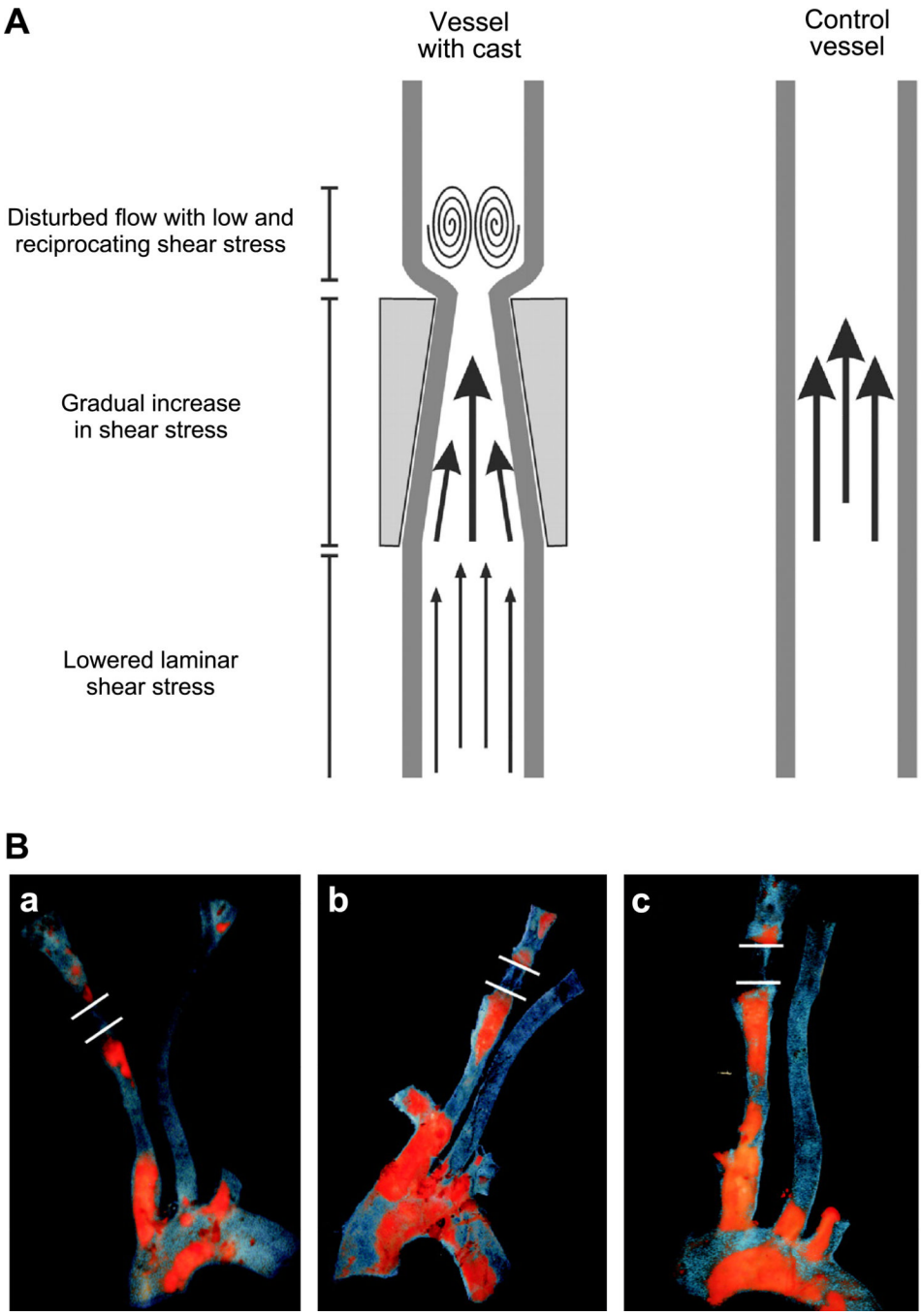


FIG. 19.

Both unidirectional low shear stress and disturbed flow with low and reciprocating shear stress induce the development of atherosclerotic lesions. *A*: schematic representation of the shear stress patterns induced by the cast. On the *right* is a straight segment of a mouse common carotid artery without a cast, which has laminar blood flow (indicated by parallel arrows). On the *left* is a a mouse common carotid artery with the cast. Upstream from the cast, shear stress is relatively low (compared with the shear stress in the control vessel) due to the flow-limiting stenosis induced by the cast. Within the cast, a gradual increase in shear stress occurs due to the tapered shape of the cast. A disturbed flow region with low and reciprocating shear stress occurs immediately downstream the cast. *B*: ApoE$^{-/-}$ mice are

instrumented with the cast 2 wk after starting the atherogenic Western diet and the specimens were obtained after 6 (*B–a*), 9 (*B–b*), or 12 wk (*B–c*) of cast placement. Whole-mount aortic arches and carotid arteries are stained with Oil red O for atherosclerotic lesions. White lines demarcate the previous position of the cast with the increased shear stress region. It is noted that atherosclerosis is induced in regions of both *1*) unidirectional low shear stress upstream the cast and *2*) disturbed flow with low and reciprocating shear stress downstream the cast. For details, see Cheng et al. (82). [From Cheng et al. (82).]

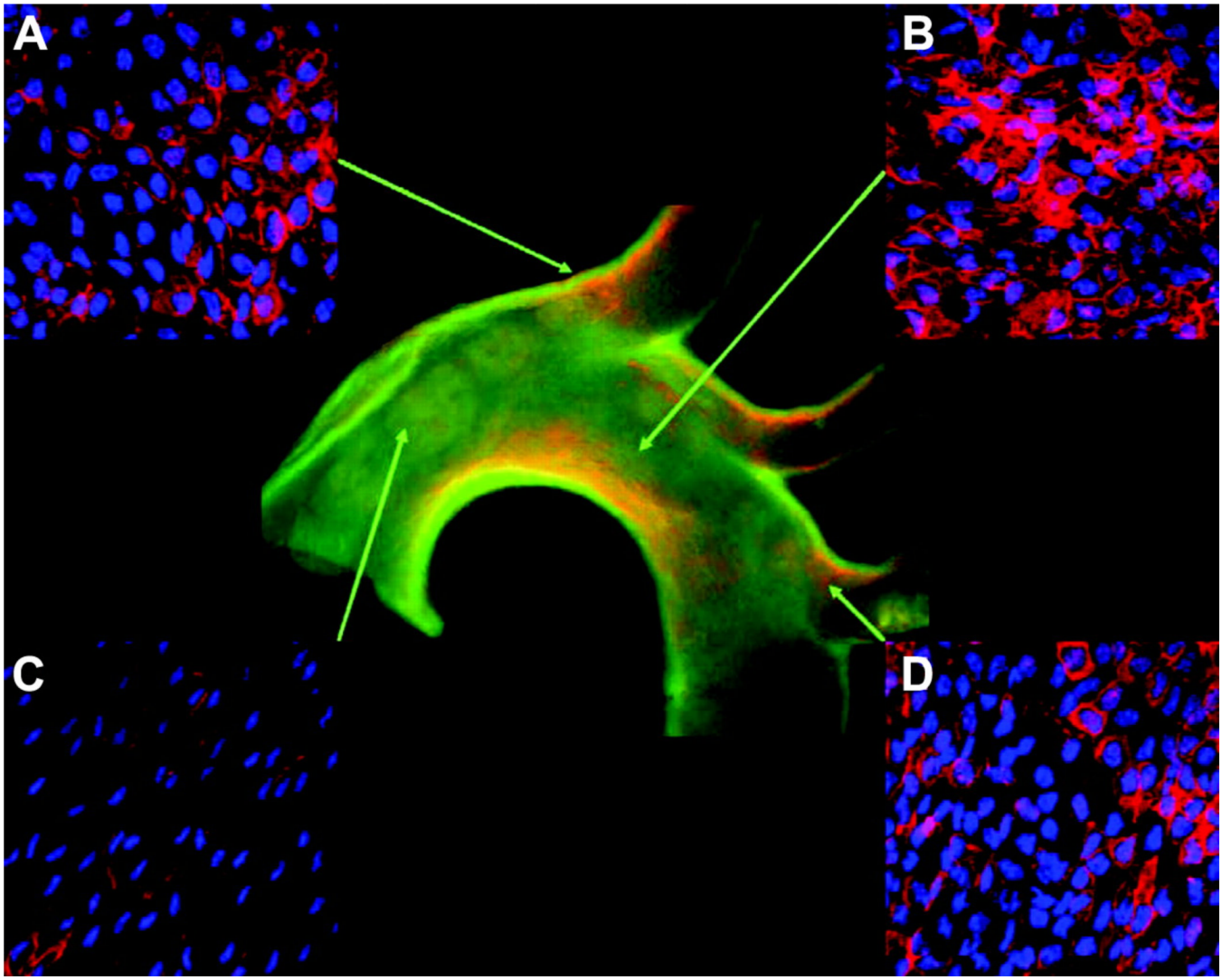


FIG. 20.

Enhanced expression of VCAM-1 along the inner curvature of the aortic arch and at the orifices of the arch branches. VCAM-1 protein expression in the mouse aortic arch is analyzed ex vivo by using immunohistochemical staining with an antibody against VCAM-1, followed by Qdot-bioconjugated secondary antibody, and two-photon excitation microscopy (center). Regions with enhanced VCAM-1 expression can be observed along the inner curvature of the aortic arch and at the orifices of the arch branches. This distribution correlates with the development of lesions (Fig. 4) and low values of mean wall shear stress (Fig. 5*B*). *Panels A*, *B*, *C*, and *D* show differential expression of VCAM-1 in different areas indicated by arrows. The lateral walls of the ascending aorta (i.e., *panel C*) are areas where there is less VCAM-1 expression, which coincides with a relatively high mean shear stress. [From Suo et al. (552).]

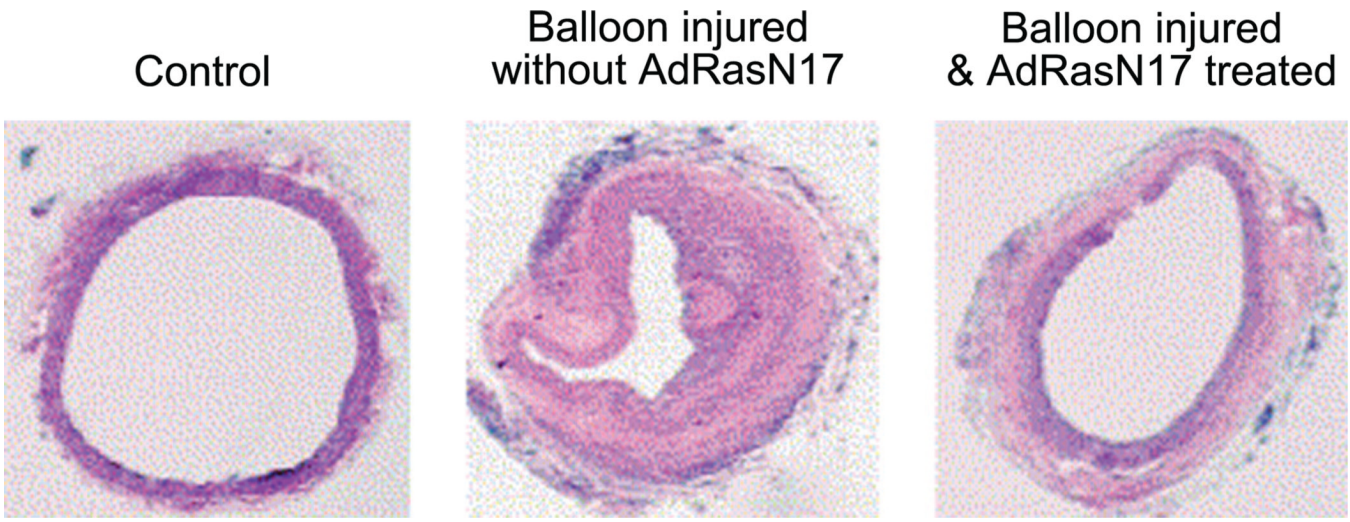


FIG. 21.

RasN17 prevents restenosis of rat common carotid artery after balloon injury. The phtographs show (*left* to *right*) the wide lumen in control artery, the severe stenosis following balloon injury without AdRasN17 (with only control AdLacZ), and the marked reduction of stenosis with vessel patency following balloon injury with AdRasN17 treatment. [From Chien (86).]

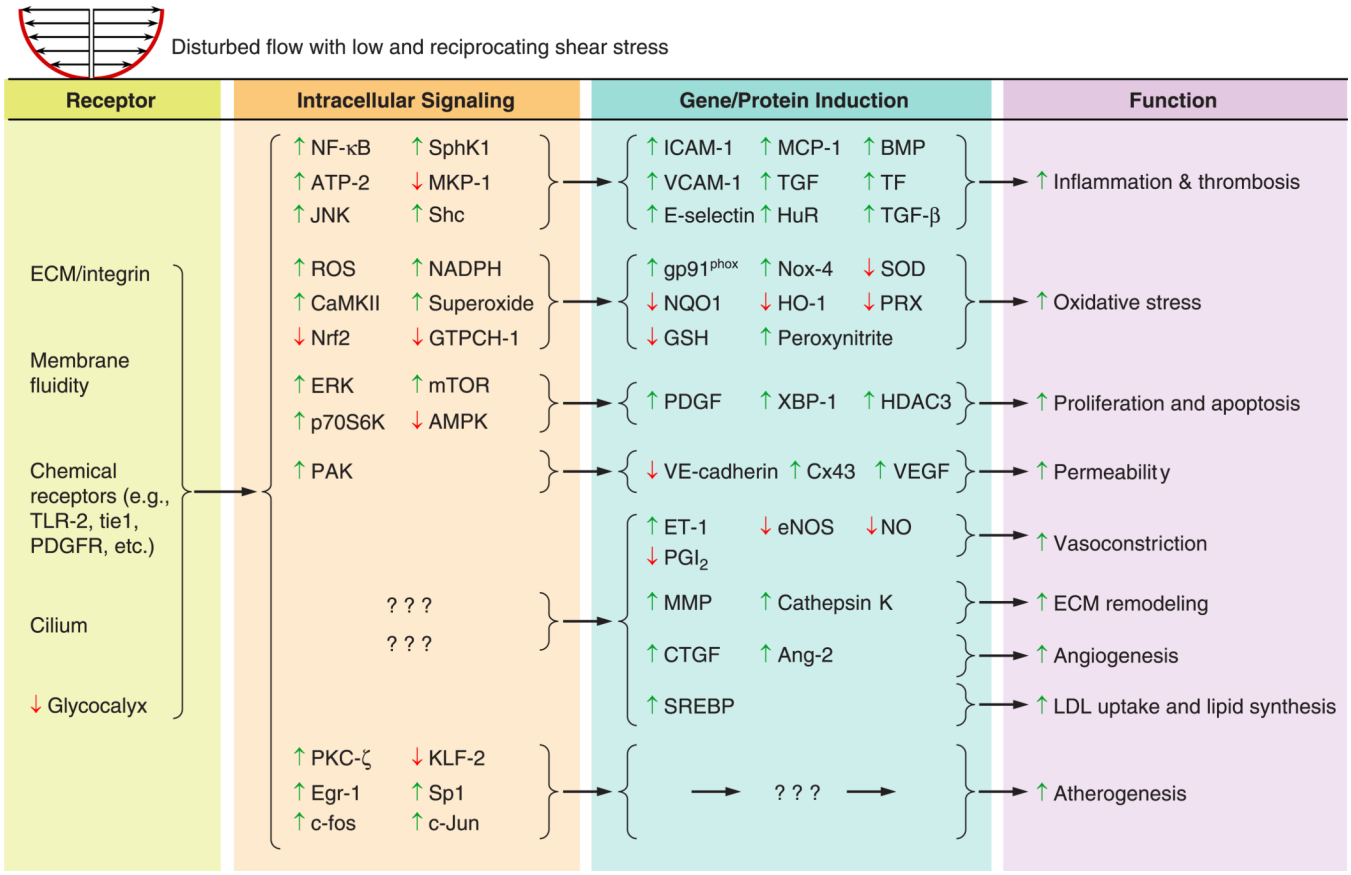


FIG. 22.

EC signaling, gene expression, and function regulated by disturbed flow. ↑, Upregulation or sustentation versus laminar flow with higher shear stress; ↓, downregulation versus laminar flow with higher shear stress. "???" indicates that the molecules responsible for mediating the signaling are still not known.

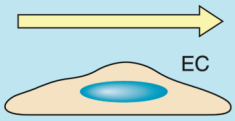
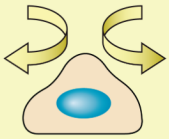
	Laminar flow / high shear stress 	Disturbed flow / low or reciprocating shear stress 
Vasoactivity	Vasodilation	Vasoconstriction
Turnover rate	Low	High
Macromolecular permeability & LDL uptake	Low	High
DNA synthesis	Low	High
Morphology	Elongated & aligned	Polygonal
Expression of adhesion molecules, inflammatory & chemokine genes	Low	High
Expression of antioxidant genes	High	Low
WBC adhesion and platelet aggregation	Inhibition	Promotion
Oxidative stress/ROS	Low	High (Sustained)
VSMC activation	Low	High
Wound repair: Endothelization	Promotion	Retardation
Heterogeneity	Low	High
Fibronectin/fibrinogen deposition	Low	High
Atherosclerosis & thrombosis	Prevention	Promotion

FIG. 23.
Summary of effects of different flow patterns and associated shear stresses on endothelial and vascular biology.

TABLE 1

A selection of studies showing the correlation between locations of atherosclerotic lesions and regions of disturbed flow in human arteries

Subject					Methods			
N	Sample source	Age	Sex	Vessel	Experimental	Modeling	Flow pattern and visualization	Reference Nos.
12	Autopsy (no history of stroke or symptoms of cerebral dis.)	27–73 (Mean: 53)	Either	Carotid artery	Angiogram, histology	Scale model, LDA	Steady (H bubble, dye injection, and washout)	644
20 (lesions)	Autopsy (no history of symptomatic cerebrovasc. dis.)	27–73 (Mean: 53)	Either	Carotid artery	Angiogram, histology	Scale model, LDA	Pulsatile, Oscillatory	311
23	Patients (with coronary heart disease risk factors and plaque in the CCA and/or CB of one side and no lesions in the contralateral carotid tree)	Mean: 55	Either	Carotid artery (Plaque/control)	Echo-Doppler	Wall shear stress = blood viscosity × blood velocity/internal diameter		217
30	Patients (no obstruct. dis.)	34–81 (Mean: 60)	Either	Coronary artery	Angiogram, histology	Velocity assessed by the rate of clearance of contrast material		494
17	Autopsy (no card. dis.)							
5	Autopsy (no card. dis.)	M: 18, 56, 61, 75 F: 51	Either	Coronary artery	High-speed cinemicrography, histology	Isolated transparent natural arteries	Steady, pulsatile (suspended tracer particles)	16
26 (patients) 74 (lesions)	Patients (treated with diet or medication over 3 yr)		Either	Coronary artery	Angiogram	FDM	Steady	207
13	Patients (with lumen obstruction <50%)	Mean: 61	M: 9 F: 4	Coronary	Intracoronary ultrasound, angiogram	Structured grid and FVM		544
	Autopsy	64	M	Abdominal aorta, Common iliac artery	Angiogram	Anatomically accurate model	Steady, pulsatile (dye injection and washout)	595
15	Autopsy (no clinical symptoms referrable to the aorta)	41–92 (Mean: 55)	M	Abdominal aorta	Angiogram, histology, quantitative morphometry	Anatomically accurate model, MRI velocimetry	Pulsatile, oscillatory	392
10	Autopsy (no history of cardiovasc. dis.)	18–40 (Mean: 34)	M: 9 F: 1	Abdominal aorta	Histology	Anatomically accurate model, LDA	Pulsatile	454
10	Autopsy (no history of cardiovasc. dis.)	18–40 (Mean: 34)	Either	Abdominal aorta	Histology	MRI velocimetry Linear-regression analysis	Pulsatile	455
26	Patients (hyperlipidemic; lipid-lowering therapy; all had either intermittent claudication or asymptomatic hypercholesterolemia combined with pathological findings at plethysmography and slight or moderate femoral atherosclerosis)	39–69	Either	Femoral artery	Cineangiography		Pulsatile (contrast injection, ZDF)	535
17	Patients (hyperlipidemic; lipid-lowering therapy; all had either intermittent claudication or asymptomatic hypercholesterolemia combined with pathological findings at plethysmography and slight or moderate femoral atherosclerosis)	39–69	M: 7 F: 10	Femoral artery	Cineangiography		Pulsatile (contrast injection, ZDF)	534

CB, carotid bulb; CCA, common carotid artery; F, female; FDM, finite difference method; FVM, finite volume method; LDA, laser-Doppler anemometry; M, male; MRI, magnetic resonance image; ZDF, zones of delayed contrast filling.

TABLE 2

Summary of studies using step-flow chamber on endothelial responses to laminar and disturbed flows

Responses	Laminar Flow (Shear Stress >10 dyn/cm^2)	Disturbed Flow (Shear Stress ~ ± 4 dyn/cm^2)	Reference Nos.
Morphology	Aligned	Round	94, 147
Actin distribution	Long and parallel stress fibers in central regions	Random and short filaments at cell periphery	94
Proliferation/DNA synthesis/mitosis	Low	High	94, 86, 148, 337, 564
Migration	Fast	Slow	259
Permeability	Low	High	458
Signaling; gene expression, and production			
Gene expression heterogeneity	Low	High	134
Connexin43	Low, continuous distribution	High, discontinuous distribution	134, 147
Nuclear factor-κB	Low	High	405
Early growth factor-1	Low	High	405
c-*fos*	Low	High	405
c-Jun	Low	High	405
Intercellular adhesion molecule-1	Low	High	88
E-selectin	Low	High	88
Tie1	Low	High	469
VE-cadherin	Continuous distribution	Discontinuous distribution	379
Sterol regulatory element binding protein	Transient activation	Sustained activation	349
WBC adhesion	Low	High	28, 88, 76, 532
WBC transendothelial migration	Low	High	76

WBC, white blood cell.

TABLE 3

In vivo correlations of in vitro responses of EC signaling and gene expression to disturbed flow at athero-prone and poststenotic areas

	In vitro					In vivo			
			Stimulus						
Signaling/Genes and Products (Expression or Activity)	**Effect of Reciprocating or Low Flow (Versus Laminar or Pulsatile)**	**Model**	**Flow type: dyn/cm^2**	**Duration (h)**	**Reference Nos.**	**Response (Versus Straight Segment or Control Vessel)**	**Segment**	**Animal/Subject**	**Refs.**
Inflammation									
ICAM-1	Increased	HUVEC in parallel-plate chamber	PF: 5 ± 5 RF: ± 5	24	72	Profound focal expression in the outer wall of the internal carotid artery and advanced lesions	Carotid artery	Patients	168
	Increased	EC in orbital shaker/parallel-plate chamber	LF: 14 Orbital: 4–12 (96–210 rpm)	6	119	Highly expressed at lesion-prone sites	Aortas	C57BL/6 mice Rabbits	269
							Ascending aorta and proximal arch	LDLR$^{-/-}$ mice	
							Aortic arch	ApoE$^{-/-}$ mice	
	Increased	BAEC in flow channel	PF: 50 ± 40 RF: ± 2.6	4	257	Highly expressed at lesion-prone sites	Aortic sinus, ascending aorta, aortic arch, and abdominal aorta	C57BL/6 mice ApoE$^{-/-}$ mice	407
	Increased	HAEC in cone-and-plate viscometer	RF: ± 5	24	536	Increased by disturbed flow induced by partial ligation	Carotid artery	C57BL/6 mice ApoE$^{-/-}$ mice p47$^{phox-/-}$mice p47$^{phox-/-}$/ApoE$^{-/-}$ mice	410
	Increased	HAEC in cone-and-plate viscometer	LF: 5, 15 RF: ± 5	24	537	Highly expressed at lesions Highly expressed in lesser curvature and orifices of arch branches	Coronary artery Aortic arch	Patients C57BL/6 mice	536 552
VCAM-1	Increased	HAEC in disturbed flow/parallel-plate chamber	LF: 13 Recirculation:< 0.01	24	50	Expressed at advanced lesions	Carotid artery	Patients	168
	Increased	HUVEC in parallel-plate chamber	PF: 5 ± 5 RF: ± 5	24	72	Highly expressed at lesion-prone sites	Aortas, Ascending aorta and proximal arch, Aortic arch	C57BL/6 mice Rabbits LDLR$^{-/-}$ mice ApoE$^{-/-}$ mice	269
	Increased	HUVEC in cone-and-plate viscometer	Athero-prone versus atheroprotective patterns form human carotid	24	115	Highly expressed at lesion-prone sites	Aortic sinus, ascending aorta, aortic arch, and abdominal aorta	C57BL/6 mice ApoE$^{-/-}$ mice	407

	In vitro					In vivo			
			Stimulus						
Signaling/Genes and Products (Expression or Activity)	**Effect of Reciprocating or Low Flow (Versus Laminar or Pulsatile)**	**Model**	**Flow type: dyn/cm^2**	**Duration (h)**	**Reference Nos.**	**Response (Versus Straight Segment or Control Vessel)**	**Segment**	**Animal/Subject**	**Refs.**
	Increased	HUVEC in cone-and-plate viscometer	Athero-prone versus atheroprotective patterns from human circulation	24	239	Increased by disturbed flow induced by partial ligation	Carotid artery	C57BL/6 mice ApoE$^{-/-}$ mice p47$^{phox-/-}$ mice p47$^{phox-/-}$/ApoE$^{-/-}$ mice	410
Highly expressed in lesser curvature and orifices of arch branches	Aortic arch	C57BL/6 mice	552						
Increased expression with reduced flow by ligation	Carotid artery	Rabbits	596						
E-selectin	Increased	HAEC in disturbed flow/parallel-plate chamber	LF: 13 Recirculation: <0.01	24	52	Expressed at advanced lesions	Carotid artery	Patients	168
	Increased	HUVEC in parallel-plate chamber	PF: 5 ± 5 RF: ± 5	24	72				
	Increased	EC in orbital shaker/parallel-plate chamber	LF: 14 Orbital: 4–12 (960–210 rpm)	6	119				
MCP-1	Increased	BAEC in flow channel	PF: 50 ± 40 RF: ± 2.6	4	257	Highly expressed near the intercostal artery orifices	Descending aorta	Rats	86
	Increased	BAEC in flow channel	LF: 25 RF: ± 3	4, 8	265				
BMPs or their antagonists	Increased	BAEC/HCAEC in cone-and-plate viscometer	LF: 15 RF: ± 5	24	71	Highly expressed at lesions	Carotid artery	Patients	46
	Increased	MAEC in cone-and-plate viscometer RF: ±5	LF: 5, 15	24	537	Coexpression of BMP-4 and the antagonists follistatin, noggin, and matrix Gla protein	Aortic arch and thoracic aorta Coronary artery	C57BL/6 mice Patients	71
						Sustained immunoreactivity of matrix Gla protein at lesions	Abdominal aorta	Patients	151
						Increased for BMP-4 by disturbed flow induced by partial ligation	Carotid artery	C57BL/6 mice ApoE$^{-/-}$ mice	410

Signaling/Genes and Products (Expression or Activity)	In vitro: Effect of Reciprocating or Low Flow (Versus Laminar or Pulsatile)	In vitro: Model	In vitro: Stimulus: Flow type: dyn/cm^2	In vitro: Stimulus: Duration (h)	In vitro: Reference Nos.	In vivo: Response (Versus Straight Segment or Control Vessel)	In vivo: Segment	In vivo: Animal/Subject	In vivo: Refs.
								p47$^{phox-/-}$ mice	
								p47$^{phox-/-}$/ApoE$^{-/-}$ mice	
						Highly expressed at lesions	Coronary artery	Patients	537
TLR-2	Increased	HCAEC in step flow chamber	LF: >5	12	161	Highly expressed in lesser curvature	Aortic arch	LDLR$^{-/-}$ mice	399
			Recirculation			Atheroprotective by TLR2 deficiency	Aortic arch	TLR2$^{-/-}$ mice	
JNK	Increased	BAEC in parallel-plate chamber	LF: 12	18	229	Higher phosphor. in lesser curvature versus greater curvature of aortic arch	Aortic arch	C57BL/6 mice	229
			RF: 0.6 ± 1.92			Higher phosphor. in carotid sinus versus straight segments	Carotid artery	ApoE$^{-/-}$ mice	
HuR	Increased	HUVEC in cone-and-plate	LF: 15	24	487	Increased in lesser curvature versus greater curvature of aortic arch, and by disturbed flow induced by partial carotid ligation	Aorta arch	C57BL/6 mice	487
			RF: ± 5				Carotid artery		
Oxidative stress									
Superoxide, NAD(P)H oxidase, H_2O_2, orperoxynitrite	Increased	HUVEC in parallel-plate chamber	LF: 5	1, 5, 24	138	Positive nitrotyrosine staining (an indicator of peroxynitrite) in bifurcations and curvatures	Coronary artery	Patients	258
			RF: ± 5						
	Increased	BAEC in a flow channel	LF: 23	4	258				
			RF: 0.02 ± 3						
	Increased	BAEC in flow channel	LF: 25	4, 8	266				
			RF: ± 3						
	Increased (Xanthine oxidase)	BAEC/MAEC in cone-and-plate viscometer	LF: 15	4	374				
			RF: ±15						
GTPCH-1	Decreased	HAEC/HUVEC in cone-and-plate viscometer	LF: 15	14	335	Decreased by disturbed flow induced by partial ligation	Carotid artery	C57BL/6 mice	335
			RF: ± 15						
Regulation of endothelial integrity/ apoptosis									
XBP-1	Increased	HUVEC in parallel-plate chamber	LF: 12	24	647	Highly expressed in branch curve and lesion areas	Aortas	ApoE$^{-/-}$ mice	647
			RF: ± 4.5						
Tie1	Increased	BAEC in a parallel-plate/step flow chamber	LF:12	16	469	Up-regulated at the (1) femoral artery and its branches, (2) aorta-renal artery junction, (3) inner aspect of the	Femoral artery, aorta-renal artery junction,	*tie1*-lacZ transgenic rats,	469

	In vitro					In vivo			
Signaling/Genes and Products (Expression or Activity)	**Effect of Reciprocating or Low Flow (Versus Laminar or Pulsatile)**	**Model**	**Stimulus**		**Reference Nos.**	**Response (Versus Straight Segment or Control Vessel)**	**Segment**	**Animal/Subject**	**Refs.**
			Flow type: dyn/cm^2	**Duration (h)**					
			Recirculation			cup-shaped cusps in the aortic side of aortic valve, (4) atherosclerotic lesions in the abdominal aorta, (5) downstream of the A/V junction in vein interposition grafts, and (6) region of flow obstruction in aneurysms.	aortic valve, abdominal aorta, vein interposition grafts, aneurysms	*tie1*-lacZ transgenic mice, ApoE$^{-/-}$ mice	
HDAC3	Increased	HUVEC in orbital shaker	0–20 with mean of 4.5 at 0.5Hz	24	643	Increased in areas in close vicinity to branching openings	Aortas	ApoE$^{-/-}$ mice	643
Regulation of endothelial permeability									
PAK	Increased	BAEC in parallel-plate flow chamber/cone-and-plate viscometer	LF: 12 Athero-prone versus atheroprotective patterns from human carotid	4	440	PAK activity correlates with VCAM-1 expression, FN deposits, and vascular permeability	Carotid artery, Aortic arch	ApoE$^{-/-}$ mice	440
Cx43	Increased	BAEC in step flow channel	LF: 13.5 Recirculation: 0–8.5	5, 16	147	Abundant at downstream edge of the ostia of branching vessels and at flow dividers	Aortas	Rats	195
						Highly expressed at lesions	Aortic arch Carotid artery	LDLR$^{-/-}$ mice Patients	314
Regulation of EC migration									
Ang-2	Increased	HUVEC/HMEC/BAEC in cone-and-plate viscometer	LF: 5, 15 RF: ± 5, ± 15	24	574	Increased in lesser curvature versus greater curvarure of aortic arch	Aortic arch and thoracic aorta	C57/BL6J mice	574
Regulation of SMC proliferation and migration									
PDGF-A, -B or receptors	Increased by TF versus LF and PF, Decreased by LF versus static	BAEC in cone-and-plate viscometer	LF: 15, 36 TF: 15 ± 0.90 PF: 12 ± 0.06–18 ± 0.29	6	361	Increased	Carotid artery	Patients	616
PDGF-DD	Increased	HUVEC/HUVSMC in cone-and-plate viscometer	Athero-prone versus atheroprotective patterns from human carotid	24	566	Increased at lesions	Aortic arch	ApoE$^{-/-}$ mice	566
Regulation of ECM									

Signaling/Genes and Products (Expression or Activity)	In vitro: Effect of Reciprocating or Low Flow (Versus Laminar or Pulsatile)	In vitro: Model	In vitro: Stimulus: Flow type: dyn/cm^2	In vitro: Stimulus: Duration (h)	In vitro: Reference Nos.	In vivo: Response (Versus Straight Segment or Control Vessel)	In vivo: Segment	In vivo: Animal/Subject	In vivo: Refs.
Cathepsin K	Increased	MAEC in cone-and-plate viscometer	LF: 15 RF: ± 5	24	461	Positive correlation with elastic lamina fragmentation	Coronary arteries with various degrees of plaques	Patients	461
MMP-9	Increased	Perfused left common porcine carotids *ex vivo*	PF: 0.3 ± 0.1, 6 ± 3 RF: 0.3 ± 3	72	200	Increased by flow cessation by ligation	Carotid artery	C57BL/6J mice	218
	Increased	MLEC/HUVEC in cone-and-plate viscometer	LF: 15 RF: ±15	6	357				
MMP-2	Increased	Perfused left common porcine carotids *ex vivo*	PF: 0.3 ± 0.1, 6 ± 3 RF: 0.3 ± 3	72	200	Increased by reduction in flow by partial outflow occlusion in injured right common carotid artery	Carotid artery	New Zealand White male rabbits	29
Vasodilator									
eNOS	Decreased	Perfused left common porcine carotids *ex vivo*	PF: 0.3 ± 0.1, 6 ± 3 RF: 0.3 ± 3	72	199	Low expression at poststenotic sites	Carotid artery constriction	eNOS-GFP transgenic mice	83
	Decreased	BAEC in flow channel	LF: 23 RF: 0.02 ± 3	4, 8	258	Decreased by disturbed flow induced by partial ligation	Carotid artery	C57BL/6 mice ApoE$^{-/-}$ mice p47$^{phox-/-}$ mice p47$^{phox-/-}$/ApoE$^{-/-}$ mice	410
	Decreased	BAEC in flow channel	LF: 25 RF: ± 3	4, 8	265				
	Decreased	Perfused BAEC tubes	LF: 10 RF: 10 ± 10	4	474				
	Decreased	Perfused BAEC tubes	PF: 6 ± 3 RF: 0.3 ± 3	4, 24	526				
	Decreased	Perfused EAhy 926 tubes	PF: 6 ± 3 RF: 0.3 ± 3	24	527				
	Decreased	HAEC in cone-and-plate viscometer	LF: 15 RF: ± 15	14	615				
	Decreased	Perfused BAEC tubes	PF: 6 ± 3 RF: 0.3 ± 3	1, 4, 24	653				
Complement inhibitory protein									

	In vitro					In vivo			
Signaling/Genes and Products (Expression or Activity)	**Effect of Reciprocating or Low Flow (Versus Laminar or Pulsatile)**	**Model**	**Stimulus**		**Reference Nos.**	**Response (Versus Straight Segment or Control Vessel)**	**Segment**	**Animal/Subject**	**Refs.**
			Flow type: dyn/cm^2	**Duration (h)**					
CD59	Decreased versus LF and no induction versus static	HUVEC/HAEC in parallel-plate chamber	LF: 12 RF: ±5	24, 48	296	Lower expression at lesser curvature of aortic arch compared with straight segments	Aortas	Murine	296
Signal transduction									
AMPK	Decreased	BAEC in parallel-plate chamber	LF: 12 RF: 1 ± 5	8	228	Lower expression at aortic arch than thoracic aorta	Aorta arch Thoracic aorta	C57BL/6J mice	228
p70S6K	Increased	BAEC in parallel-plate chamber	LF: 12 RF: 1 ± 5	8	228	Higher expression at aortic arch than thoracic aorta	Aorta arch Thoracic aorta	C57BL/6J mice	228
MKP-1	Increased by LF versus static	HUVEC in parallel-plate chamber	LF: 12	24, 48	642	Lower expression in lesser curvature than greater curvature, Sparing of lesions in MKP-1$^{-/-}$ mice	Aortas	C57BL/6 mice MKP-1$^{-/-}$ mice	642
Shc	Increased	BAEC in parallel-plate chamber	LF: 12 RF: ±6.5	18	350	Higher phosphor. at aortic arch compared with straight ascending aorta	Aortas	C57BL/6 mice	350
Transcription factor									
KLF-2	Decreased	HUVEC in cone-and-plate viscometer	Athero-prone versus atheroprotective patterns from human carotid	24	444	Low expression at branches and poststenotic sites	Abdominal aorta bifurcation, common iliac artery, carotid artery bifurcation, aortic arch, carotid artery constriction	Patients ApoE$^{-/-}$ mice	145
	Decreased	HUVEC in parallel-plate chamber	PF: 12 ± 4 RF: 0.5 ± 4	24	600	Decreased by disturbed flow induced by partial ligation	Carotid artery	C57BL/6 mice ApoE$^{-/-}$ mice p47$^{phox-/-}$ mice p47$^{phox-/-}$/ApoE$^{-/-}$ mice	410
						No or low expression at branches and poststenotic sites	Abdominal aorta and celiac artery, Abdominal aorta constriction	Rats	600
Nrf2	Decreased	HUVEC in cone-and-plate viscometer	Athero-prone versus atheroprotective patterns from human carotid	24	116	Decreased Nrf2 nuclear localization in endothelium in lesser curvature of the arch versus straight portion of thoracic aorta	Aortic arch and thoracic aorta.	C57BL/6 mice	116
NF-κB	Increased	HUVEC in cone-and-plate viscometer	Athero-prone versus atheroprotective patterns from human carotid	24	115	Activated at fibrotic-thickened intima/media and atheromatous areas of lesion	Atherosclerotic aortas, normal arteries, veins	Patients	48

	In vitro					In vivo			
Signaling/Genes and Products (Expression or Activity)	**Effect of Reciprocating or Low Flow (Versus Laminar or Pulsatile)**	**Model**	**Stimulus**		**Reference Nos.**	**Response (Versus Straight Segment or Control Vessel)**	**Segment**	**Animal/Subject**	**Refs.**
			Flow type: dyn/cm^2	**Duration (h)**					
	Increased	HUVEC in cone-and-plate viscometer	Athero-prone versus atheroprotective patterns from human circulation	24	239	Highly expressed at lesion-prone sites	Ascending aorta and arch	C57BL/6 mice LDLR$^{-/-}$ mice	234
	Increased by 2 versus 16 (dyn/cm^2)	HAEC in parallel-plate chamber	LF: 2, 16	0.5–24	387	Robust p65 localization in lesser curvature versus greater curvature	Aortic arch	ApoE$^{-/-}$ mice	239
	Increased	BAEC/HUVEC in parallel-plate chamber	LF: 12	18	437	Activated (inhibited by PAK-Nck blocking peptides)	Carotid sinuses	C57BL/6 mice	437
			RF: 1 ± 12			Activated in experimental hypercholesterolemia	Coronary arteries	Pigs	629
Egr-1	Increased	HUVEC in step flow chamber	LF:12		405	Highly expressed at lesions	Carotid artery,	Patients	369
			Recirculation				Aortas	LDLR$^{-/-}$ mice	
Others									
Heat shock protein 60	Decreased by low shear versus high shear.	HUVEC in cone-and-plate viscometer	LF: 0–50	24	252	Lower expression in reduced shear versus increased shear regions by ligation	Carotid artery	Lewis rats	252

BAEC, bovine aortic endothelial cell; HAEC, human aortic endothelial cell; HCAEC, human coronary artery endothelial cell; HMEC, human microvascular endothelial cell; HUVEC, human umbilical vein endothelial cell; HUVSMC, human umbilical vein smooth muscle cell; MAEC, mouse aortic endothelial cell; MLEC, murine lymphoid endothelial cell; LF, laminar flow; RF, reciprocating flow; PF, pulsatile flow; TF, turbulent flow; FN, fibronectin.