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EDITORIAL COMMENT

In Vivo Assessment of Local Intravascular Hemodynamics and Arterial Morphology to Investigate Vascular Outcomes

A Growing Field Coming of Age*

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The arterial system, and in particular, the endothelium, is a complex "organ" capable of sensing its environment and adjusting itself to maintain optimal structure and function so that adequate blood flow and nutrients are delivered to organs and distal tissues. The normal arterial wall is capable of undergoing major reshaping as evidenced by arterial adaptations during physiological processes. One of the principal signals to which the endothelium is exposed, and, consequently, that influences endothelial structure and function, is the endothelial shear stress (ESS), the frictional drag of blood flowing tangentially across the endothelial surface of the arterial wall. An abnormal change in the ESS on the wall activates feedback mechanisms that return these ESS forces to "normal" values. If ESS is altered from its physiological state, the arterial diameter responds by changing in such a way as to restore ESS to the physiological range. In normal arteries, high ESS elicits an expansive remodeling response, whereas low ESS elicits a constrictive one. Much of the flow-mediated physiological adaptation is genetically influenced (1).

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In pathological vascular conditions, the process of sensing local hemodynamic and morphological characteristics and responding to them is typically more complex and may even become maladaptive. The pathobiological consequences associated with alterations of ESS in animals and patients predisposed to atherosclerosis have been studied extensively in vitro and ex vivo for many decades (2–7). Low and oscillatory ESS conditions lead to a phenotypic switch toward a proatherogenic and proinflammatory phenotype, whereas physiological ESS conditions lead to quiescence in the vascular wall, and high ESS is associated with platelet activation and adhesion (5,7). Shear stress is typically low in areas such as the inner aspect of curvatures, downstream from an obstruction, and at the outer waist of a bifurcation; ESS is generally high on the outer portion of curves and at the throat of an obstruction.

The nature of ESS patterns can be very complex and can change dramatically as vascular anatomy, arterial remodeling responses, and pathobiology change (8). As an atherosclerotic lesion develops and progresses, for example, new local hemodynamic environments are created that, in turn, influence new pathobiological consequences. A vicious cycle may be created whereby progressive changes in plaque and wall morphology and, consequently, local flow patterns lead to further increases in local atherosclerosis.

Until recently, the local intravascular characteristics of anatomy and ESS could only be investigated in vitro or ex vivo (3,9,10). New methodologies now exist that enable ESS and vascular remodeling patterns to be characterized in vivo and suggest uses that may ultimately be suitable for clinical purposes (11–14).

Applications for Measurement of Local ESS and Vascular Morphology

Predict development and progression of coronary artery disease. One of the major applications of this new ability to characterize local ESS and arterial remodeling patterns in vivo has been to risk-stratify individual coronary plaques, that is, to identify areas where coronary artery plaque is likely to develop, progress, and potentially form high-risk thin-cap fibroatheromas that are prone to rupture (8,14–19). Areas of low ESS uniquely and predictably manifest coronary plaque and there is a direct relationship between the magnitude of local low ESS and the magnitude of local lipid accumulation, inflammation, and plaque formation (19). Endothelial shear stress is the driving pathobiological mechanism responsible for much of plaque formation and progression and for remodeling behavior. The hemodynamic factors responsible for frank plaque rupture are under ongoing investigation. Serial studies in large animal models and pilot studies in man suggest that these approaches may be able to predict areas that will become responsible for causing a new clinical event (8,15,18,19), and a large-scale trial in humans is underway (PREDICTION [Prediction of Progression of Coronary Artery Disease and Clinical Outcome Using Vascular Profiling of Shear Stress and Wall Morphology] trial).

Evaluate conformability of intracoronary stent design. Recent studies have employed detailed computational fluid dynamics to characterize local ESS patterns associated with stent strut design to minimize local areas of disturbed flow and low ESS, as those areas are associated with atheroprone and procoagulant flow conditions that also retard endothelializa-

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tion (20). In this issue of *JACC: Cardiovascular Interventions,* Gomez-Lara et al. (21) use the conceptual approach of characterizing the local vascular environment associated with scaffold design of stents to gauge the potential clinical value of bioresorbable versus metallic stent scaffolds as a function of stent conformability. They retrospectively compared 102 patients who received a metal scaffold stent (Multi-Link Vision stent, Abbott Laboratories, Abbott Park, Illinois) with 89 patients who received a bioresorbable polymer scaffold stent (everolimus-eluting stent) (BVS) (Abbott Vascular, Santa Clara, California). Stents of both scaffold designs were of similar size and were deployed in the routine manner. The investigators evaluated the arterial segment that included the stented region and measured arterial curvature and angulation before, during, and immediately after stent deployment using quantitative coronary angiography techniques and special software to assess local arterial geometry. Curvature was defined as the infinitesimal rate of change in the tangent vector at each point of the lumen centerline, and angulation was defined as the angle in degrees that the tip of an intracoronary guideline would need to reach the distal part of a coronary bend. The change in angulation after stent deployment was significantly less with the bioresorbable polymer scaffold stent compared with the metal scaffold stent ($p = 0.03$), and the change in coronary artery curvature from before to after stent deployment showed a nonsignificant trend favoring the bioresorbable polymer scaffold stent ($p = 0.06$). There was also significantly less hinging movement of the artery between systole and diastole with the bioresorbable scaffold compared with the metal scaffold. In a multivariate model, the type of scaffold independently predicted the change in both artery curvature ($p = 0.01$) and artery angulation ($p = 0.02$) following stent deployment. The investigators conclude that the bioresorbable scaffold was associated with better conformability and, therefore, preservation of better local blood flow characteristics and less likelihood of in-stent restenosis or stent thrombosis. The putative clinical benefits of less disturbed local blood flow patterns associated with the bioresorbable scaffold remain speculative, however, because this investigation was an acute observational study only. As the investigators acknowledge, it will be necessary to assess the curvature and angulation of the stented area in medium- and long-term follow-up, as well as the angiographic and clinical outcomes in these patients, to determine if the preservation of more physiologic local blood flow patterns from the bioresorbable scaffold are indeed more vasculoprotective than the metallic scaffold. Calculation of local ESS patterns within these stents would also enhance the characterization of the local geometric consequences of the different stent designs in a much more precise manner than the simple indexes of artery curvature and angulation.

Assessment of neointimal response following elution of different drugs from stents. In this issue of *JACC: Cardiovascular Interventions,* Papafaklis et al. (22) report another innovative use of understanding the local arterial hemodynamic environment. They compared the neointimal thickness response 6 months after implantation of either sirolimus- or paclitaxel-eluting stents to the response of bare-metal stents. They used the local ESS, derived from 3-dimensional reconstruction of the coronary artery stented area and computational fluid dynamics, as a provocative stimulus to gauge the efficacy of the antiproliferation medication. They observed that neointimal thickness was significantly lower following deployment of drug-eluting stents compared with bare-metal stents ($p < 0.001$) and that maximum neointimal thickness was lower in sirolimus-eluting stents compared with paclitaxel-eluting stents ($p = 0.025$). Local ESS was indeed an independent predictor of neointimal thickness. Only sirolimus elution was associated with attenuation of the neointimal thickness response to low ESS, whereas paclitaxel elution and bare-metal stents exhibited a similar relationship of local ESS to the magnitude of neointimal thickness. The investigators speculate that sirolimus elution, when compared with paclitaxel elution, may have incremental benefits by abrogating the adverse local response to low ESS, which could potentially amplify the neointimal response in certain lesions with high-risk geometry. They speculate further that these differences in inhibition of neointimal formation are likely responsible for the differences in adverse clinical outcomes observed in large-scale clinical trials comparing the different drugs eluted.

Potential Future Applications of Assessing Local Hemodynamic Patterns

Assessment of high-risk plaque in carotid artery or the aorta. Atherosclerosis in the internal carotid artery constitutes a major source of cerebral embolism. The intensely proatherosclerotic nature of local flow disturbances associated with the carotid bifurcation and the carotid bulb have been extensively demonstrated in ex vivo and in vitro studies (3,9). Recent innovative studies have used in vivo flow-sensitive 4-dimensional magnetic resonance imaging to characterize detailed carotid anatomy and blood flow in healthy individuals and patients with carotid atherosclerosis and have enabled detailed calculation of local ESS (23). Patterns of adversely disturbed local flow are readily evident by such studies, and areas with disturbed flow patterns correlate closely with the localization and severity of atherosclerosis. Similar analyses have been performed from magnetic resonance images of the thoracic and abdominal aorta (24,25). In vivo risk-stratification of individual plaques in the carotid artery or the aorta may be enormously valuable to identify which atherosclerotic areas are most in jeopardy of rapid enlargement, proclivity to form clot and subsequent thromboembolism, or to rupture.

Noninvasive assessment of coronary atherosclerosis progression. Identification of areas of local coronary atherosclerosis development and progression has heretofore required invasive techniques of coronary angiography and intravascular ultrasound.

New noninvasive techniques to acquire lumen and vascular dimensions in 3-dimensional space may be able to identify high-risk plaque and enable identification of adverse low ESS areas. There are promising early results using coronary computed tomographic angiography to accomplish these goals (26,27). If such techniques are effective and safe, as the resolution of computed tomography increases and the dose of required radiation exposure decreases, it may be possible to develop strategies of computed tomographic angiography to identify which patients are at risk for developing high-risk lesions on a trajectory toward plaque rupture.

Conclusions

The field of identifying the local ESS and anatomic vascular patterns to assess or predict vascular outcomes has evolved dramatically over the past few years. Although previous methodologies limited investigations to in vitro or ex vivo approaches, new methodologies allow in vivo investigations that can be performed with readily available equipment. Data acquisition necessary to calculate local ESS patterns and vascular morphology is routine, but post-processing of images and computational analyses of lumen and vascular structures are time-consuming and labor-intensive, such that they are not yet suitable for routine real-time clinical management. Methods continue to evolve at a very rapid pace, however, and the concept of risk-stratification of individual atherosclerotic plaques or individual vascular areas may soon become routine. It is likely that such individual plaque-based or artery-based approaches will dramatically enhance the precision and clinical benefit of our therapeutic strategies.

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REFERENCES

1. Korshunov VA, Berk BC. Strain-dependent vascular remodeling: the "Glagov phenomenon" is genetically determined. Circulation 2004; 110:220–6.
2. Caro CG, Fitz-Gerald JM, Schroter RC. Arterial wall shear and distribution of early atheroma in man. Nature 1969;223:1159–60.
3. Ku DN, Giddens DP, Zarins CK, Glagov S. Pulsatile flow and atherosclerosis in the human carotid bifurcation. Positive correlation between plaque location and low oscillating shear stress. Arteriosclerosis 1985;5:293–302.
4. Ku D. Blood flow in arteries. Annu Rev Fluid Mech 1997;79:399–434.
5. Malek AM, Alper SL, Izumo S. Hemodynamic shear stress and its role in atherosclerosis. JAMA 1999;282:2035–42.
6. Gimbrone MA Jr., Topper JN, Nagel T, Anderson KR, Garcia-Cardeña G. Endothelial dysfunction, hemodynamic forces, and atherogenesis. Ann N Y Acad Sci 2000;902:230–9, discussion 239–40.
7. Chatzizisis YS, Coskun AU, Jonas M, Edelman ER, Feldman CL, Stone PH. Role of endothelial shear stress in the natural history of coronary atherosclerosis and vascular remodeling: molecular, cellular, and vascular behavior. J Am Coll Cardiol 2007;49:2379–93.
8. Koskinas KC, Feldman CL, Chatzizisis YS, et al. Natural history of experimental coronary atherosclerosis and vascular remodeling in relation to endothelial shear stress: a serial, in vivo intravascular ultrasound study. Circulation 2010;121:2092–101.
9. Zarins CK, Giddens DP, Bharadvaj BK, Sottiurai VS, Mabon RF, Glagov S. Carotid bifurcation atherosclerosis. Quantitative correlation of plaque localization with flow velocity profiles and wall shear stress. Circ Res 1983;53:502–14.
10. Asakura T, Karino T. Flow patterns and spatial distribution of atherosclerotic lesions in human coronary arteries. Circ Res 1990;66:1045–66.
11. Ilegbusi OJ, Hu Z, Nesto R, Waxman S, et al. Determination of blood flow and endothelial shear stress in human coronary artery in vivo. J Invasive Cardiol 1999;11:667–74.
12. Slager CJ, Wentzel JJ, Schuurbiers JC, et al. True 3-dimensional reconstruction of coronary arteries in patients by fusion of angiography and IVUS (ANGUS) and its quantitative validation. Circulation 2000;102:511–6.
13. Giannoglou GD, Chatzizisis YS, Sianos G, et al. In-vivo validation of spatially correct three-dimensional reconstruction of human coronary arteries by integrating intravascular ultrasound and biplane angiography. Coron Artery Dis 2006;17:533–43.
14. Fukumoto Y, Hiro T, Fujii T, et al. Localized elevation of shear stress is related to coronary plaque rupture: a 3-dimensional intravascular ultrasound study with in-vivo color mapping of shear stress distribution. J Am Coll Cardiol 2008;51:645–50.
15. Stone PH, Coskun AU, Kinlay S, et al. Effect of endothelial shear stress on the progression of coronary artery disease, vascular remodeling, and in-stent restenosis in humans. in vivo 6-month follow-up study. Circulation 2003;108:438–44.
16. Wentzel JJ, Janssen E, Vos J, et al. Extension of increased atherosclerotic wall thickness into high shear stress regions is associated with loss of compensatory remodeling. Circulation 2003;108:17–23.
17. Cheng C, Tempel D, van Haperen R, et al. Atherosclerotic lesion size and vulnerability are determined by patterns of fluid shear stress. Circulation 2006;113:2744–53.
18. Stone PH, Coskun AU, Kinlay S, et al. Regions of low endothelial shear stress are the sites where coronary plaque progresses and vascular remodelling occurs in humans: an in vivo serial study. Eur Heart J 2007;28:705–10.
19. Chatzizisis YS, Jonas M, Coskun AU, et al. Prediction of the localization of high-risk coronary atherosclerotic plaques on the basis of low endothelial shear stress: an intravascular ultrasound and histopathology natural history study. Circulation 2008;117:993–1002.
20. Jimenez JM, Davies PF. Hemodynamically driven stent strut design. Ann Biomed Eng 2009;37:1483–94.
21. Gomez-Lara J, Garcia-Garcia HM, Onuma Y, et al. A comparison of the conformability of everolimus-eluting bioresorbable vascular scaffolds to metal platform coronary stents. J Am Coll Cardiol Intv 2010;3:1190–8.
22. Papafaklis MI, Bourantas CV, Theodorakis PE, et al. The effect of shear stress on neointimial response following sirolimus- and paclitaxel-eluting stent implantation compared with bare-metal stents in humans. J Am Coll Cardiol Intv 2010;3:1181–9.
23. Harloff A, Albrecht F, Spreer J, et al. 3D blood flow characteristics in the carotid artery bifurcation assessed by flow-sensitive 4D MRI at 3T. Magn Reson Med 2009;61:65–74.
24. Frydrychowicz A, Stalder AF, Russe MF, et al. Three-dimensional analysis of segmental wall shear stress in the aorta by flow-sensitive four-dimensional-MRI. J Magn Reson Imaging 2009;30:77–84.
25. Harloff A, Nussbaumer A, Bauer S, et al. In vivo assessment of wall shear stress in the atherosclerotic aorta using flow-sensitive 4D MRI. Magn Reson Med 2010;63:1529–36.
26. Rybicki FJ, Melchionne S, Mitsouras D, et al. Prediction of coronary artery plaque progression and potential rupture from 320-detector row prospectively ECG-gated single heart beat CT angiography: lattice Boltzmann evaluation of endothelial shear stress. Int J Cardiovasc Imaging 2009;25:289–99.
27. van der Giessen AG, Schaap M, Gijsen FJ, et al. 3D fusion of intravascular ultrasound and coronary computed tomography for in-vivo wall shear stress analysis: a feasibility study. Int J Cardiovasc Imaging 2010;26:781–96.

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