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## Cardiology Is Flow

Yoram Richter, PhD; Elazer R. Edelman, MD, PhD

Panta rhei. (*Everything flows*).<sup>1</sup>

**C**ardiology is about flow. The primary purpose of the cardiovascular system is to drive, control, and maintain blood flow to all parts of the body. Flow dictates the form and function of the heart and blood vessels through ontogenic and phylogenic development, the structural and functional consequence of repair, and in its end stages, remodeling and response to failure. Flow should therefore be a primary focus by which we explain where lesions form, why they degrade and decompensate, and how we grade the extent of restoration of function after vascular intervention. Yet this is not the case. Flow is not a standard part of our clinical lexicon. Few reliable and consistent means of measuring flow exist. Despite early use of surrogate flow markers (eg, TIMI frame count), we do not quantify flow restoration after interventions. Moreover, there is simply no agreement as to the aspect or degree of flow that is most important in lesion development or functional recovery.

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#### Flow and Atherogenesis

The nonhomogeneous nature of atherosclerosis has been appreciated since the earliest days of research in the field.<sup>2</sup> Certain arterial segments develop profound lesions, whereas adjacent regions seem completely spared. Neither properties of blood nor local cellular and molecular biological events can vary significantly on such length scales to explain such spatial heterogeneity. Local flow properties can change on these scales (Figure 1), and alterations in local flow pattern—for example, the intricate vectorial description of fluid speed and direction across the entire cross section of the lumen—were invoked as a possible explanation for the observed scatter in pathology.<sup>2–5</sup> In this context, lesion distribution is not random but aligns with, and accumulates within, areas of flow disturbances such as those that occur around tight curves, bifurcations, and in areas already beset by atheroscle-

rosis. Flow disturbances are therefore ubiquitous; they are a fundamental feature of the vascular system. An entire field of study arose correlating disease with its overlying flow pattern.<sup>6–9</sup> Several factors, including low shear stress, oscillatory (bidirectional) flow, and regions of eddies and/or boundary-layer separation, have repeatedly been shown by numerous researchers, using both numerical and observational techniques, to be the prime candidates for wreaking havoc on vascular biology.<sup>10–13</sup> Other workers then simulated these same factors in vitro to show their possible effects on a cellular level.<sup>14–16</sup>

*Everything flows and nothing abides, everything gives way and nothing stays fixed.*<sup>1</sup>

In this issue of *Circulation*, Cheng et al<sup>17</sup> take this one step further by artificially varying flow conditions in vivo. They show that lesions indeed develop consistent with a priori predictions based on flow patterns. In their elegant experiment, a cast alters vessel geometry to create 3 distinct regions of altered flow in the carotid arteries of apolipoprotein E–knockout mice. Areas were created with *reduced* shear stress relative to the native state, *elevated* shear stress, and *directionally oscillatory* shear stress. The pattern of lesions was compared with the contralateral artery in which a non–geometry-altering cast was placed. Each of the 3 flow regimens has a distinct effect on the quantity, composition, and nature of atherosclerotic disease. Intriguingly, it is not the absolute level of shear stress that determines the vascular response. Rather than low or high shear stress, Cheng et al<sup>17</sup> found that reduced or elevated shear stress exerted the effect on local vascular biology. Thus, changes in flow patterns can be more important than the flow patterns themselves in producing potentially deleterious effects on vascular biology. Indeed, in their study, though shear stress was changed, it was never particularly low or excessively high. This is important in that previous studies in mice have been questioned given the higher shear stress typically seen in mice relative to humans. By shifting the emphasis from the static concept of shear stress to the dynamic concept of shear stress alterations, this criticism is significantly muted.

#### Flow and Angiology

These findings are attractive to those who examine fluid dynamics at the interface of vascular biology. They are also essential clinically. This report should force us once again to attempt to introduce flow into our description of lesions, determination of form of intervention, and delineation of device effects. Obstructive lesions are anatomic curiosities until they alter flow such that they appreciably raise vascular resistance and then they become clinically relevant. The objective of vascular interventions, pharmacological or me-

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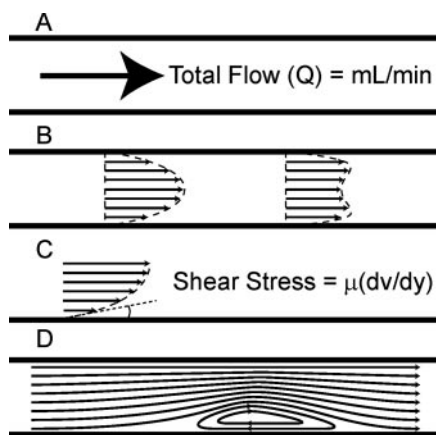
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**Figure 1.** Basic concepts in fluid flow. A, Total flow is the volume of fluid that flows through the artery per unit time. B, The flow profile is the vectorial description of fluid velocity at each point in the cross section of the lumen. The profile can be parabolic (as seen on the left) but usually takes up much more complex forms (as seen on the right). C, Shear stress is the force per unit area exerted on the vessel wall by the flowing blood and is proportional to the viscosity of blood and the derivative of the fluid velocity. D, Streamline descriptions of flow pattern show the paths of each particle within the flow and are especially convenient for highlighting flow disturbances such as this region of recirculation. Such flow disturbances commonly arise in arterial bends and bifurcations.

chanical, is to relieve flow obstruction. Every time a vasoactive drug is administered, a lesion is inflated, or a stent is implanted, flow changes occur both locally and globally within the arterial tree. Flow changes can occur distally or proximally to an intervened lesion or even in parallel vessels. By lowering resistance at one location in the vasculature, resistance and flow at other locations can increase or decrease in much the same way that physiological flow regulation is achieved. The flow pattern in remote locations can vary considerably, introducing regions of pulsatile flow, boundary layer separation, and raised/lowered shear stress where none existed previously. Nevertheless, we do not define clinical intercessions in terms of flow; instead, we rely almost exclusively on anatomic descriptions.

In the absence of the ability to measure vascular flow, we continue to describe vascular health dimensionally. Angiography, however, can be misleading. The study by Cheng et al<sup>17</sup> highlights this issue. Although the geometry and diameter are identical in both proximal carotid arteries of their mice, the total flow and hence the shear stress through these arteries are decidedly different. As a result, the pattern of atherosclerosis is entirely different in the contralateral vessels within the same animal. Furthermore, although angiography can teach us something about total flow—for example, that all other things being equal, bigger is better—it can teach us nothing about the flow pattern. By merely describing the lumen diameter at every point, we entirely miss the internal pattern of eddies, boundary layer separations, and other phenomena that are much more tightly related to disease formation and progression than is total flow. Again, the study by Cheng et al<sup>17</sup> provides an illustrative example: The region of recirculation immediately downstream from the cast has a normal diameter and would thus be termed “normal” by

angiography. However, this region is by far the worst in terms of extent and vulnerability of disease.

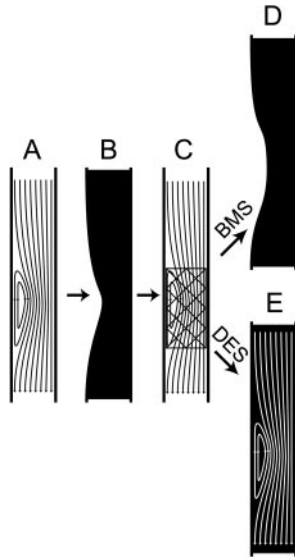
### Why Not Flow?

A central consideration in the incorporation of the concept of flow into clinical practice is our inability to reliably describe flow in most of the arteries of interest. Angiographic techniques such as TIMI frame count and myocardial blush are valuable but nonspecific. Doppler ultrasound can measure total flow but can only be applied in a handful of blood vessels that are relatively superficial. The Doppler flow wire provides an assessment of total intravascular flow. However, the manner of measurement forces assumptions about the flow profile. This profile is ordinarily assumed to be parabolic. In practice, however, most arteries of interest have profiles that are far from parabolic. This is particularly true in the most important regions, which typically include one type or another of flow disturbance. Consequently, the results of flow wire measurements can be misleading. A common characteristic of all of the technologies mentioned above is that they only describe total flow and give no information about the sometimes more important flow pattern.

Newer, more advanced imaging modalities such as magnetic resonance angiography offer the potential for incorporating flow measurement together with delineation of anatomy. If clinical demand is present, flow wire-type devices may be reengineered with extended functionality and precision, perhaps in conjunction with fluoroscopy or intravascular ultrasound. Although fluoroscopy will likely remain the primary guide for vascular intervention, the appreciation for the importance of flow can add insight into the mechanism of disease and individualize clinical decision-making. Studies of the type by Cheng et al<sup>17</sup> and an increased collaboration between physicians and flow-oriented engineers might provide a means of concentrating less on restoring a patient’s anatomy to a group norm and more on tailoring individual therapy on the basis of flow restoration.

### Flow-Guided Vascular Therapeutics

What implications do these sorts of findings have in daily practice? One could argue that the association of certain flow disturbances with atherosclerotic burden and vulnerability is interesting but academic at best. Arterial geometries may be predictive of ultimate lesion formation, but no one has yet intervened in the native geometry in an attempt to prevent the primary disease. In our research laboratory, however, we have shown that the association of flow disturbance with vascular fate can be directly extrapolated to the sister-process to atherosclerosis—that is, restenosis.<sup>18</sup> Viewed in this light, alterations in flow pattern become critically important as we strive to further reduce the number of reinterventions after mechanical interventions. Ironically, the drug-eluting stent (DES) revolution that has occurred over the past few years makes this particular problem even more complex (Figure 2). Flow disturbances inside a stent lead to intimal hyperplasia, which encroaches on the lumen, and to restenosis.



**Figure 2.** DES masking of flow disturbance. Localized flow disturbance (A), typically seen at tight bends or in and around bifurcations, will ultimately lead to angiographically detectable lesions (B), as the study by Cheng et al<sup>17</sup> shows. When the lesion is stented (C), the obstructive lesion is displaced but the flow disturbance is reestablished, although the latter cannot be seen on angiography. For bare metal stents (BMS), this will ultimately lead to angiographically detectable restenosis (D). In contrast, with intimal hyperplasia nearly eliminated, DES give the angiographic appearance of a healthy vessel (E). However, flow disturbance remains (depicted here in white but angiographically undetectable). This “effective” lesion raises vascular resistance, and flow within the artery is diminished.

Thus, by generating intimal hyperplasia that we can see, flow disturbance that we could not see now has an angiographically visible manifestation. By nearly completely inhibiting intimal hyperplasia, the DES masks the continued presence of flow disturbance inside the stent. The naïve view would be to ask what difference flow disturbance makes if it does not affect restenosis. We point out, however, that a region of flow disturbance consumes energy and forces mainstream flow to go around it. An effective obstruction is created in this way, which can raise vascular resistance and thereby lower flow just as an actual physical protrusion into the lumen would. Thus, in the setting of acute flow disturbance, bare metal stents ultimately lead to physical obstructions, whereas DES leave only effective obstructions but with similar effects on total flow. To be sure, the patient with a DES is not worse off than the patient with a bare metal stent; however, the angiographic or intravascular ultrasound appearance of being better off can be misleading. Only actual flow measurement can decisively determine clinical benefit in this setting.

*Men do not know how that which is drawn in different directions harmonizes with itself. The harmonious structure of the world depends on opposite tension like that of the bow and the lyre.<sup>1</sup>*

All of this raises multiple possibilities for knowledge extension. We live in an era of active collaboration among the models of the physical scientist, biological insight of the vascular scientist, and clinical perspective and reality imposition of the clinician. Perhaps we can now ask whether flow should be not only a marker of system performance, but a metric of interventional success and perhaps even a therapeutic target. If we accept the premise that the main, perhaps only, goal of intervention is to increase flow, shouldn't flow be the benchmark by which interventional success is assayed? Even using today's tools, flow rates and changes in perfusion can be described. These tests can then serve as the basis of a new breed of clinical tests and trials—ones that seek to optimize interventional strategy rather than device designs. The explosion of clinical trials over the past few years has created a situation whereby our knowledge of individual drug and device properties far exceeds that of our therapeutic strategy. Having always been a technology-driven field, perhaps it is now time to answer more fundamental device-independent questions, such as: Which vessels should be opened to maximize benefit in a multilesion situation? What is the relative importance of specific branches and when does the benefit from opening them no longer exceed the potential risk? What effect, if any, does revascularization in one location have on progression of disease and flow in others? Is a reduction in local flow resistance always accompanied by an improvement in global perfusion? Should the benefit from pharmacological attempts at atherosclerotic lesion regression focus on flow restoration, not just reduction in vessel obstruction? By using flow as a metric for success, we can begin to answer these questions. Furthermore, increased clinical interest will drive development of better modalities by which to describe flow.

Studies such as the one by Cheng et al<sup>17</sup> should refocus attention on these more global issues so that we can return to what cardiology is truly about—optimization of flow.

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### Disclosures

None.

### References

1. Ηρακλειτος (Herakleitos; Heraclitus) of Ephesus (c. 535–475 BC). Quoted by Plato in *Cratylus*, 402a, and by Diogenes Laertius in *Lives of the Philosophers* Book IX, section 8.
2. Texon M. A hemodynamic concept of atherosclerosis, with particular reference to coronary occlusion. *AMA Arch Intern Med.* 1957;99:418–427.
3. Caro CG, Fitz-Gerald JM, Schroter RC. Arterial wall shear and distribution of early atheroma in man. *Nature.* 1969;223:1159–1160.
4. Fry DL. Acute vascular endothelial changes associated with increased blood velocity gradients. *Circ Res.* 1968;22:165–197.
5. Glagov S, Zarins C, Giddens DP, Ku DN. Hemodynamics and atherosclerosis: insights and perspectives gained from studies of human arteries. *Arch Pathol Lab Med.* 1988;112:1018–1031.
6. Bharadvaj BK, Mabon RF, Giddens DP. Steady flow in a model of the human carotid bifurcation, II: laser-Doppler anemometer measurements. *J Biomech.* 1982;15:363–378.

7. Bharadvaj BK, Mabon RF, Giddens DP. Steady flow in a model of the human carotid bifurcation, I: flow visualization. *J Biomech.* 1982;15:349–362.
8. Asakura T, Karino T. Flow patterns and spatial distribution of atherosclerotic lesions in human coronary arteries. *Circ Res.* 1990;66:1045–1066.
9. Friedman MH, Kuban BD, Schmalbrock P, Smith K, Altan T. Fabrication of vascular replicas from magnetic resonance images. *J Biomech Eng.* 1995;117:364–366.
10. Pritchard WF, Davies PF, Derafshi Z, Polacek DC, Tsao R, Dull RO, Jones SA, Giddens DP. Effects of wall shear stress and fluid recirculation on the localization of circulating monocytes in a three-dimensional flow model. *J Biomech.* 1995;28:1459–1469.
11. Sabbah HN, Khaja F, Brymer JF, Hawkins ET, Stein PD. Blood velocity in the right coronary artery: relation to the distribution of atherosclerotic lesions. *Am J Cardiol.* 1984;53:1008–1012.
12. Moore JE Jr, Xu C, Glagov S, Zarins CK, Ku DN. Fluid wall shear stress measurements in a model of the human abdominal aorta: oscillatory behavior and relationship to atherosclerosis. *Atherosclerosis.* 1994;110:225–240.
13. He X, Ku DN. Pulsatile flow in the human left coronary artery bifurcation: average conditions. *J Biomech Eng.* 1996;118:74–82.
14. Davies PF, Remuzzi A, Gordon EJ, Dewey CF Jr, Gimbrone MA Jr. Turbulent fluid shear stress induces vascular endothelial cell turnover in vitro. *Proc Natl Acad Sci U S A.* 1986;83:2114–2117.
15. Davies PF. Flow-mediated endothelial mechanotransduction. *Physiol Rev.* 1995;75:519–560.
16. DePaola N, Gimbrone MA Jr, Davies PF, Dewey CF Jr. Vascular endothelium responds to fluid shear stress gradients [published erratum appears in *Arterioscler Thromb.* 1993;13:465]. *Arterioscler Thromb.* 1992;12:1254–1257.
17. Cheng C, Tempel D, van Haperen R, van der Baan A, Grosveld F, Daemen MJAP, Krams R, de Crom R. Atherosclerotic lesion size and vulnerability are determined by patterns of fluid shear stress. *Circulation.* 2006;113:2744–2753.
18. Richter Y, Groothuis A, Seifert P, Edelman ER. Dynamic flow alterations dictate leukocyte adhesion and response to endovascular interventions. *J Clin Invest.* 2004;113:1607–1614.

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