TO NEW STUDENTS OF VASCULAR physiologists, it sometimes comes as a surprise that blood flow in large conduit arteries such as the femoral and brachial arteries ceases to move forward and, indeed, reverses direction throughout the cardiac cycle. This is true under a variety of conditions in humans and other species. We still recall our initial reluctance in switching to the use of Doppler ultrasound (from the more-established venous occlusion plethysmography), an unease that was closely linked to an inability to overcome our preconception that blood should always be moving forward, in an antegrade fashion, in these “garden-hose variety” vessels, rather than moving backward, or retrograde, during portions of diastole, as clearly indicated in our Doppler velocity tracings. Fifteen years later, as we introduce new students to the use of Doppler ultrasound in our respective laboratories, we instruct them that oscillatory flow during the cardiac cycle is generally the norm and indicative of a subject who is in a relaxed state. Over those same 15 years, research on endothelial cell function in a variety of models ranging from cell culture to isolated vessels to in vivo studies has lead to a consensus that the pattern of blood flow and the resulting oscillatory shear patterns in these conduit vessels has a primary influence over endothelial cell function and vascular health and may be linked to atherosclerosis. Thus the presence of retrograde blood flow in peripheral vessels and the resulting retrograde shear of the endothelium has taken on considerable importance related to the understanding of vascular aging and peripheral artery disease progression.

A number of studies in the last year have documented the presence of retrograde shear patterns in humans (2) and demonstrated that these patterns are sensitive to posture (11), hydrostatic gradients (3), exercise modalities (8), and other hemodynamic manipulations. Furthermore, when these retrograde shear patterns are manipulated, they produce short-term changes in endothelial function as determined by measures such as flow-mediated vasodilation (9, 11). Such work has strongly corroborated findings from more reductionist experiments.

In this issue of the American Journal of Physiology-Heart and Circulatory Physiology, Padilla et al. (4) expand on this line of work by reaching into the bag of sympathoexcitatory tricks and selecting a set of maneuvers, all of which produce considerable activation of sympathetic nerves to muscle vascular beds but that vary in regard to whether they are associated with elevations in arterial pressure or not. Thus, using a well-designed protocol, they have managed to explore the relationship among sympathetically mediated vasoconstriction, arterial pressure, and the resulting changes in the antegrade-retrograde flow and shear profiles in the brachial artery of healthy humans. Using classic interventions such as lower body negative pressure, the cold pressor response, and the exercise pressor response, they document an intriguing interaction in which elevations in sympathetic vasoconstrictor nerve activity promote retrograde flow and shear, whereas concurrent elevations in arterial pressure appear to mitigate the effect of sympathoexcitation on the flow and shear pattern. Their data speak to the role of sympathetic nerves in augmenting retrograde shear in inactive limbs during exercise and a number of other physiological settings.

When we review these new results and the literature on which it builds, it becomes apparent that the autonomic and hemodynamic milieu are capable of generating a wide range of shear profiles from entirely antegrade (e.g., carotid and cerebral arteries) to slightly oscillatory (e.g., resting brachial) to markedly oscillatory (e.g., brachial artery during upright cycling). Many research groups have the tools to inventory these patterns, and the pioneers in the area are far along in this task. Yet, we seldom consider the question of why there is such a thing as retrograde flow at all and whether we can identify a “unified model” for its generation. As vascular physiologists, we often think of vascular beds as functioning like a simple fluid-filled tube of a set length and variable diameter. This model is what drove our preconceptions that there should always be antegrade flow, as even during a very low diastolic pressure dip; surely the arterial perfusion pressure is maintained above venous pressure. Perhaps we need to move to a more complicated model such as a Starling resistor and its “vascular waterfall” analogy to identify the origin of retrograde flow and shear. This concept was explored extensively by Madger and others in the 90s and has promise for explaining many of the observations related to retrograde flow in conduit arteries, if one assumes that 1) there are compliant vessels between the site of measurement and the downstream Starling resistor, 2) the Starling resistor has a “critical pressure” that determines the collapse of the downstream pathway, and 3) critical pressure falls with vasodilation (6) and increases with vasoconstriction (7). If these assumptions hold true, then overall antegrade flow would be present whenever arterial perfusion pressure is above the critical pressure, but if the upstream pressure dips below the critical pressure (as would generally happen during diastole), forward flow will cease and any blood volume residing in downstream compliant vessels (yet proximal to the Starling resistor) may be translocated retrogradely as central arterial pressure falls further. Thus it stands to reason that what determines the balance between retrograde flow and antegrade flow (and the resulting shear patterns) is likely the balance between central arterial pressure and the microvascular critical closing pressure. Furthermore, one would predict that a rise in sympathetic vasoconstrictor nerve activity should increase the critical closing pressure, so more of the cardiac cycle falls below the critical pressure (i.e., less antegrade flow, and more retrograde flow), whereas increasing central arterial pressure shifts the system so that more of the cardiac cycle falls above the critical pressure (i.e., more antegrade flow, and less retrograde flow). Along these lines, when Thijssen et al. (9) used a venous collecting cuff set to 25,
50, or 75 mmHg to create incremental levels of retrograde flow and shear in the brachial arterial tree, they were in essence creating a quasi-shearfall model and demonstrating its impact on retrograde shear and endothelial function. It seems that the new work by Padilla et al. (4) and others (8–10) leads us back to the work of Shrier and Magder (6, 7) to find a unified model for retrograde shear. Can this more complex model lead us into the future and predict important outcomes?

If our model for hemodynamics must be more complex to understand the generation of retrograde flow, perhaps too we should ask ourselves whether we are adequately diligent in our assessment of retrograde shear. We still rely heavily on the fluid dynamic equations developed by Poiseuille, which are based on constant laminar flow of Newtonian fluid, an inherently nonphysiological condition. Padilla et al. (4) rely on the shear rate calculation that is derived from the Poiseuille equations, in which shear rate is proportional to the mean blood velocity across the vessel divided by the diameter of the vessel. As a field, we have put much faith in the validity of the Poiseuille equations even under conditions of oscillatory flow of non-Newtonian blood. While this may approximate the shear rate and reassure us that we are doing proper experimental controls (5), in reality, we do not truly know what the wall shear is during oscillatory flow. Much of the kinetic energy apparent in antegrade-retrograde mean and peak velocities may be dissipated between “layers” of non-Newtonian fluid, such that the near-wall shear may be a much dampened version of the oscillations observed midstream. Furthermore, Cinthio et al. (1) have documented a substantial longitudinal movement of the carotid arterial wall during the cardiac cycle that is in the direction of antegrade blood flow during systole but that is followed by a distinct retrograde movement in late systole. A similar movement was reported in the brachial artery, a movement that has the potential to either augment or diminish endothelial shear depending on the phase relationship to oscillatory flow.

What is the future of retrograde shear? We are at the earliest stages of investigating factors related to the directionality of shear and its influence on endothelial function and health. Padilla et al. (4) have set the stage for future inquiries regarding the influence of the sympathetic nervous system as well as other vasoactive signals on the generation of retrograde shear on the endothelium in human health, physical activity, and pathophysiology. As we move forward, we may need to relearn the discoveries of prior generations. And occasionally, we may need to take a step back and question our underlying models and assumptions to step forward toward the innovations that may prove necessary to define the true nature of the signals that engender endothelial health and disease.

REFERENCES