Two recent reports, including one published in this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, illuminate a critical role for fluid shear stress in triggering specific early steps in developmental programs in the vascular endothelium. The studies by Chen and colleagues use C3H10T1/2 cells, which are a stable cell line with features of primitive mesenchyme, to demonstrate that shear stress induces differentiation toward the endothelial lineage. Ando and colleagues observed similar effects of flow in embryoid body-derived Flk1-expressing cells, which are well-characterized progenitors for endothelial and hematopoietic lineages. These reports raise provocative points about shear forces in regulation of differentiation programs that lead to blood vessel formation.

Our understanding of the role of biomechanical forces in embryonic development is limited, but some general principles are beginning to emerge. Initial steps in defining the body plan are determined in part through shear-dependent regulation of left-right patterning in the mouse embryo. Normal cardiac morphogenesis in zebrafish embryos requires cues from intracardiac fluid forces, and abnormalities similar to those found in some congenital heart diseases occur when these forces are inappropriately attenuated. Although flow has generally been invoked as a stimulus for remodeling of primary capillary plexus into mature vasculature, little is known mechanistically about how this might occur. The reports by Ando and Chen and their colleagues are the first to invoke specific developmental properties for fluid shear stress within the vascular compartment.

The dogma of vascular development is built around a role for growth factor signaling and environmental cues (especially hypoxia) as the key stimuli for induction of vascular progenitors and eventual assembly of mature blood vessels. Differentiation of progenitor cells toward the endothelial lineage is the first detectable step in the vascular developmental program, and signals via the bone morphogenetic protein, hedgehog, vascular endothelial growth factor, and fibroblast growth factor families have been implicated in these early events. Tissue hypoxia activates a cellular program via stabilization of members of the hypoxia-inducible factor family of transcription factors. This in turn activates a cell-autonomous differentiation program and also stimulates the secretion of vascular endothelial growth factor to elicit a paracrine developmental signal. The present studies suggest that shear forces should be included among the factors that define where and when vascular precursors enter a differentiation pathway, although this will be difficult to prove in vivo until we know more about the sensors for shear in endothelial cells (and their precursors) and how these mechanotransduction pathways activate the developmental program.

It is also self-evident that shear forces are not an initiating event in vasculogenesis, because shear is dependent on the presence of some vasculature to allow blood flow to occur. Perhaps shear serves as a signal to allow multipotential cells adjacent to primitive vascular structures to differentiate during the vascular remodeling system. These or other functions of flow-dependent vascular differentiation can be tested and compared with, for example, growth factor–dependent differentiation, once the tools are available to selectively block or modulate early activation pathways downstream of the flow signal. In this regard, it is interesting to consider the
possibility that nitric oxide generation may be a critical immediate consequence of shear forces during vascular development, as it is in adult blood vessels. If one accepts this premise, then the consequences of impaired nitric oxide signaling during vascular development are instructive. As has been recently reported, inhibition of nitric oxide generation in cultured mouse embryos does not appreciably affect the earliest steps in endothelial cell differentiation, but instead disrupts yolk sac vessel maturation at the primary plexus stage. If nitric oxide generation at this stage of embryonic development is dependent on flow within the vasculature, then one may surmise that flow-mediated endothelial differentiation contributes to vascular remodeling and size determination. Consistent with such a model, impairment of flow in quail embryos by excision of the heart impairs arteriovenous differentiation of the primary capillary plexus.

The study by Chen and colleagues in this issue of ATVB reminds us of the elegant principle that developmental processes are recapitulated in adult pathophysiology (Figure). In this case, shear forces exert a role in blood vessel assembly by directing the maturation of vascular progenitors, and the ability to sense these shear forces in adulthood is redeployed to monitor flow-dependent vascular tone. When this process is aberrant, vascular dysfunction and atherosclerosis ultimately result. Given recent data linking circulating endothelial progenitors with modulation of the response to vascular injury, one is led to wonder whether the effects of shear on the differentiation status of endothelial progenitor cells contribute to the progression of vascular disease in areas of disturbed flow. These studies, which enlighten our understanding of developmental pathways activated by shear forces in vascular precursors, also raise some interesting issues about adult pathobiology that will warrant much additional consideration in future investigations.

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**References**


Even Flow: Shear Cues Vascular Development
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