The Continuum of Risk
Vascular Pathophysiology, Function, and Structure
Alan T. Hirsch, MD; Aaron R. Folsom, MD, MPH

What factors place people at risk for developing cardiovascular disease as they grow from youth to adulthood? How do both physiological and epidemiological investigations contribute to the development of the evidence that can support or refute current hypotheses regarding the development of atherosclerosis? How can the interplay of differing study designs improve our understanding of atherosclerosis?

Atherosclerosis is a systemic disease that is the leading cause of death in the developed world and leads to carotid artery, coronary artery, and peripheral arterial atherosclerotic syndromes. Inasmuch as atherosclerotic diseases affect as many as 64 million adults in the United States, considerable health care resources have been deployed to provide care for those affected. Past research findings have contributed to considerable advances in survival for individuals who have overt heart disease, stroke, and peripheral arterial disease, yet the continued aging of the population implies that the prevalence of each atherosclerotic disorder will increase in the decades ahead. In this context, investigations that provide insights into disease mechanisms and that define how vulnerability to atherosclerosis is established are now particularly valuable.

The pathophysiology of atherosclerosis is known to be dependent on multiple hereditary and environmental factors. It is presumed that these genetic and acquired factors contribute in a complex manner to a progressive pathophysiological process that causes a normal artery to develop progressive endothelial dysfunction. Loss of normal endothelial function is hypothesized to be a fundamental step in the atherosclerotic disease process. In this conceptual model, the iterative exposure of endothelium to risk factors leads sequentially to endothelial dysfunction, followed by intimal-medial thickening, overt manifestations of atherosclerosis, development of arterial stenoses, and ultimately to plaque rupture and endovascular thrombosis. This sequence of events has become central to current theories of atherosclerosis. Yet how do we know that this sequence is accurate?

Arterial health is maintained by an intact endothelium. This single cell layer serves as a biosynthetic shield that produces both vasodilator and vasoconstrictor paracrine factors, as well as factors that mediate hemostatic pathways. Vascular homeostasis and vascular health are defined by the preservation of this normal endothelial function. The critical role of endothelial function has been carefully evaluated in studies of the role of the vasodilator endothelium-derived nitric oxide (NO) in health and disease, in both animal and clinical studies.

Additional factors also contribute to the regulation of endothelial health. Regulation of NO synthase (NOS) is maintained by levels of an endogenous inhibitor known as asymmetrical dimethylarginine (ADMA). Furthermore, by blocking NO generation, ADMA initiates and promotes processes involved in atherogenesis, plaque progression, and plaque rupture. Endothelial “risk” also is conferred by increased vascular oxidative stress, which accelerates the degradation of NO. Hemostatic factors, including tissue factor pathway inhibitor, and Von Willebrand factor, may serve either as markers of endothelial dysfunction or as contributors to this dysfunction.

Biobehavioral factors, including diet and exercise, are also known to affect endothelial function. For example, dietary factors (e.g., the isoflavones genistein and daidzein) may alter vascular reactivity in selected hypercholesterolemic cohorts. Processes that directly injure endothelium or that impair NO bioactivity or synthesis are known to be proatherogenic. Endothelial function is diminished in individuals exposed to risk factors that are known to be associated with atherosclerosis.

Individual exposure to a range of risk factors does not define biological destiny, however. The heterogeneity of human biology implies that a complex interplay of factors may foster the translation of risk to the development of disease. Thus, in any population exposed to comparable risk, overt atherosclerotic disease may develop in some individuals, but not in others. Exposure of a population to the traditional risk factors (e.g., age, hypercholesterolemia, obesity, atherogenic diet, hypertension, diabetes mellitus, and tobacco use) is known to increase cardiovascular risk. Similarly, many new risk factors (e.g., fibrinogen, metabolic syndrome, and lipoprotein [a]) are associated with an in-
creased probability of atherosclerotic events in populations. Overall, both classic and novel risk factors appear to impair endothelial vasodilator function by causing direct damage to NO biosynthetic and related pathways.10

The role of classic and novel risk factors in the development of human disease, as derived from experiments in tissue culture, animal models, and small prospective human investigations, is not adequately informative to ensure that putative biological pathways are important in populations. In this context, and despite the proliferation of knowledge that now more than adequately describes the major vascular biological mechanisms of atherosclerosis, the role of such potential mechanisms must be confirmed in human populations. This investigational approach uses observations derived from bench research, population-based observational (longitudinal) epidemiological studies, and interventional clinical trials to evaluate the role of each risk factor as a contributor to the incidence or prevalence of overt atherosclerotic cardiovascular disease.11 With these 2 approaches, observation of the impact of a risk factor on disease development (longitudinal studies) or intervention to blunt the impact of the factor (interventional clinical trials) can provide useful information on relevant primary arterial outcomes. Such studies can relate each risk factor to structural or functional outcomes or to clinical disease end points (eg, atherosclerotic symptoms, ischemic events, hospitalization, or death). Inasmuch as these latter end points occur relatively late in the disease process and occur relatively infrequently, prospective investigations may also observe the impact of risk markers on surrogate end points for clinically relevant events. Such risk markers might include measurement of levels of inflammatory factors (eg, C-reactive protein), diminution of renal function, coronary artery calcium, increased arterial intimal-medial thickness (IMT), or left ventricular hypertrophy. These risk markers are useful as they have been related to the increased development of clinical cardiovascular disease. The characterization of the importance and causality of risk factors and risk markers in the development of vascular disease is fundamental to the design of most cardiovascular epidemiological investigations (Table).

These relationships may be best understood in study designs that permit vascular biological principles to be evaluated in conjunction with both physiological and structural measurements in population-based surveys (Figure). Such linkages can offer insights that relate population-based risk factors to the development of risk markers, events, or both. Tools that measure arterial structure and function can now permit the assessment of diminished synthesis of endothelial NO by the measurement of a blunted reactive hyperemic response to brachial artery occlusion. These measurements of “flow-mediated vasodilation” can be safely and repeatedly performed.12–14 Similarly, the use of high-resolution noninvasive ultrasound-based imaging techniques can provide early evidence of altered arterial structure, such as increased IMT.15–18 The measurement of classic risk factors, endothelial function, and arterial structure in a single

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*Elevated C-reactive protein is a risk marker, but whether it is a risk factor remains uncertain.

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Conceptual translation of cardiovascular risk to population risk. Insights into the natural history of atherosclerosis require integration of data from multiple experimental designs that ideally link vascular biology to vascular pathophysiology to population-based studies.
prospective investigation can create robust links between these pathways.

In this issue of Circulation, Juonala et al share data from the Cardiovascular Risk in Young Finns study.19,20 This study applied a combined prospective and cross-sectional design that permits some conclusions to be made that lend credence to current theories of atherosclerosis. The authors initially recruited 3596 individuals enrolled at 3 to 18 years old, assessed risk factor exposure sequentially, and obtained both carotid and brachial artery ultrasound studies from a large fraction of their original population (2109 healthy adults aged 24 to 39 years). This study design permitted the authors to relate the risk of developing structural arterial disease, as measured by the carotid IMT, to measures of brachial artery endothelial function.

Their data demonstrate that at least in this large Finnish cohort, measurements of brachial endothelial function are inversely correlated with measures of IMT. This correlation would have been anticipated from past clinical investigations and is not a novel finding. The preservation of endothelial function, however, was associated with the protection of these individuals from developing structural arterial disease, as defined by an increased IMT. Conversely, patients with endothelial dysfunction (impaired flow-mediated vasodilation) showed the expected associations between risk factors and IMT.

The Juonala et al article therefore supports but does not yet prove the concept that the physiological health of the endothelium is central to the structural health of the artery. An increased level of confidence in this thesis would require longitudinal study of this temporal relationship, essentially providing an arterial natural history in which endothelial dysfunction might be demonstrated to consistently precede arterial structural change. These data give rise to a series of questions that will require focus in future investigations. First, most of the data in the Cardiovascular Risk in Young Finns study were cross-sectional. Additional prospective population-based studies should confirm this central finding, which suggests that despite exposure to classic risk factors that might increase IMT (or other markers of vascular structure), endothelial dysfunction is a necessary step before the development of structural arterial disease. If this is the case, then what genomic or environmental factors confer protection on endothelial function in those otherwise at risk? Does modification of these risk factors in youth protect against subsequent development of increased IMT and overt atherosclerosis? Or, alternatively, does a global risk factor burden exist that leads inevitably to endothelial dysfunction and arterial remodeling?

Second, the central observation of this article, that traditional risk factors appear not to be associated with increased IMT in people with enhanced flow-mediated dilatation (FMD), must be confirmed in a larger population sample. This finding should not yet be considered definitive. This may yet be the result of chance because of the small sample size of the cohort with optimal endothelial function and the absence of a true statistical test of interaction. Third, at a time when the contribution of obesity to cardiovascular risk is increasing internationally, the positive association of obesity with FMD noted by Juonala and colleagues remains unexplained. Fourth, the deployment of physiological testing in epidemiological studies shows great promise. This promise can best be kept if these measures themselves can be made more reproducible. Large epidemiological studies face significant challenges in their use of measures of FMD and other risk markers because of the persistence of significant within-person variability, as demonstrated by the large confidence limits for FMD displayed in this study. Finally, our current knowledge base is inadequate to explain regional differences in arterial structure and function. In other words, the propensity of carotid, coronary, renal, and lower-extremity arteries to develop atherosclerosis is not identical based on risk-factor exposure. There is no reason a priori to hypothesize that the risk factor-arterial function/remodeling relationship is identical among the carotid, coronary, renal, and lower-extremity arterial circulations.21,22 Future studies should bear in mind this inherent heterogeneity of risk from the affected arterial circulation. Answers to some of these questions may be forthcoming from large prospective investigations, including the Framingham Heart Study, the Multi-Ethnic Study of Atherosclerosis,23 and the Coronary Artery Risk Development in Young Adults study.24

Despite these insights, the data from this investigation do not imply that measurement of either IMT or FMD in youth or adults plays any defined role in altering atherosclerosis risk management in populations. Clinical prudence and the economic realities of health care delivery should demand that the deployment of new arterial imaging or functional tests in practice be linked to proof that performing such tests reliably alters population-based outcomes.25 These data do not yet exist for these modalities.

If we are to ensure that the insights from basic science maximally achieve translation to population-based health improvements and diminution of disparities in health care, then efforts to design trials that bridge the gap between vascular biology and population-based health will be increasingly needed. Insights to achieve this goal can best be achieved when investigators use a range of techniques that have the potential to relate vascular biology, arterial physiology, and epidemiology into well-designed prospective observational studies and interventional trials. In this manner, the promise to diminish the risk of developing cardiovascular disease might be achieved as our population ages from youth to adulthood.

References


**KEY WORDS:** Editorials ■ atherosclerosis ■ cardiovascular diseases ■ epidemiology ■ risk factors
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