Atherosclerotic disease is a primary cause of cardiovascular morbidity and mortality. This disease is generally undiagnosed before the onset of symptoms or complications. Experimental and clinical evidence indicate that inflammation is central to the initiation and progression of atherosclerosis. Therefore, vascular inflammation may serve as a potential marker of the disease process itself. Although potentially useful in risk stratification, the current systemic markers of inflammation lack sufficient disease specificity to be used satisfactorily as screening tools in cardiovascular disease. The inaccuracy of current inflammatory markers may reflect the fact that these markers are neither derived primarily from the vascular wall nor produced primarily by cells involved in the vascular inflammatory process. Furthermore, they may signal inflammation in a number of different organs and tissues, which may or may not have direct implications for the vasculature. Because of heterogeneity of the disease phenotype in the population, a single marker may not provide sufficient biological information for an accurate assessment of vascular damage, and, therefore, it may be more interesting to look into a cluster of inflammatory markers. Human studies support an association between inflammatory gene polymorphisms and subclinical and clinical cardiovascular disease.

The predictive value of arterial stiffness or 1:elasticity for cardiovascular morbidity and mortality has now been very well established. Arterial stiffness is determined by endothelial integrity of the vascular wall, vascular smooth muscle tone, vascular remodeling, and the vascular matrix. There is now evidence that inflammation may contribute to vascular stiffness in apparently healthy individuals and in disease. Increased arterial stiffness has been noted in the offspring of hypertensive parents before an elevation in blood pressure, raising the possibility that early vascular inflammation and associated reduced NO bioavailability may lead to increased stiffness, which may contribute to the development of hypertension, especially systolic hypertension. During the last few years, several articles have been published suggesting that single nucleotide polymorphisms in genes coding for proteins, such as the renin-angiotensin-aldosterone system, endothelial NO synthase, and heat-shock C-reactive protein are related to arterial stiffness measures.

In this issue, Schnabel et al report the association among 12 circulating inflammatory biomarkers and single nucleotide polymorphisms with mean arterial pressure and a variety of arterial stiffness measures, including central pulse pressure, forward and reflected pressure wave, carotid-femoral pulse wave velocity, and augmentation index, in a community-based cohort. Their results showed that inflammatory markers explained minor additional variability in these arterial stiffness measures. The authors recognized the limitations of their study. The middle-aged-to-elderly cohort study that they examined may not be optimal to look after the genetic associations. The Framingham study is almost entirely white, so the validity of extrapolating these results to other races/ethnicities may not be possible. Therefore, these findings must be validated in other cohorts.

Previous studies evaluated potential genetic determinants of brachial blood pressure in traditional terms and did not separately consider true mean arterial pressure and the components (forward and reflected wave) of pulse pressure. Genetic association studies have shown that a significant number of gene polymorphisms may modulate increases of pulse pressure. The authors identified 7 previous genome-wide association studies that scanned the genome for association with high pulse pressure. There was evidence that there might be ethnic diversity regarding the genetic basis of pulse pressure. Pulse pressure provides only an approximation of arterial stiffness, because it may be influenced by other factors, such as age and ventricular ejection. Their findings led to the conclusion that the specific components of blood pressure and arterial load might have separate genetic determinants. The linkage for mean arterial pressure in a region not related to pulsatile measures suggested that the steady component of arterial load, which depends on cardiac output and peripheral resistance, may be modulated by a different set of genes from those that are related to large artery stiffness.

The genomic analysis of the Framingham study cohort demonstrated that heritability estimates were moderate for reflected and forward wave amplitude and mean arterial pressure. Arterial stiffness measures, mean, and pulsatile components of blood pressure were heritable and appeared to have genetic determinants that might be linked to separate genetic loci on chromosomes 8 and 15 in humans. Forward and reflected pressure wave amplitude contributed in a different way to systolic and diastolic blood pressure. Therefore, evaluation of distinct components of hemodynamic load may lead to novel insights into the genetic determinants of hypertension and various other diseases related to blood.
pressure and vascular function, such as atherosclerosis, stroke, and heart failure.

Gene expression profiling of human atherosclerosis has led to the identification of individual genes involved in atherosclerosis and has, to a lesser extent, allowed the relative significance of pathways involved in atherosclerosis. Most expression profiling studies of human atherosclerosis used experimental groups of 3 to 5 human vascular specimens from surgery or autopsy. Carotid and coronary arteries were most often used. These analyses suggested that the differentially expressed genes were involved in inflammation, cell turnover, matrix degradation, lipid metabolism, coding for matrix proteins, or originated from smooth muscle cell proliferation or dedifferentiation.

The large artery structural changes that characterize the atherosclerotic process are dependent for their development on endothelial dysfunction, which permits cell adhesion and wall infiltration. Inflammation facilitates that infiltrative process and, thus, would be expected to be associated with the severity of structural change. There is more evidence that the atherosclerotic disease occurs in a temporal sequence. Endothelial dysfunction will initially lead to changes in the function of the pool of the small arteries. Inflammation together with endothelial dysfunction will lead to functional and structural changes of the conduit arteries as identified by large artery stiffness. A key determinant of vascular inflammation is the increased generation of reactive oxygen species beyond genetic and environmental factors.

Future studies of changes in elastic properties over time in relation to changes of inflammatory markers and their genetic variants would be more compelling. These changes could be expressed as a risk trajectory and should be related to cardiovascular outcome. The use of different parameters of pulse wave velocity and wave reflections as complementary measures is more useful and informative in the assessment of arterial stiffness and ventricular-vascular interactions rather than using the two as alternatives. The detection of preclinical disease of the arterial wall may improve our ability to predict subsequent risk of atherosclerotic disease.

Disclosures
None.

References
Genetic Variants of Inflammatory Markers and Arterial Stiffness
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