Consequences of vascular aging: concepts for the clinician

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The incidence and prevalence of cardiovascular disease continue to rise with the increasing number and proportion of elderly individuals in the general population and particularly in the patient population with cardiovascular disease. An understanding of the physiologic changes associated with vascular aging is an important component of the treatment of older individuals because these changes alter the substrate upon which disease is superimposed and in so doing alter its presentation, severity and response to therapeutic interventions.

Age-associated changes in vascular properties can be divided into two categories: those which increase central vascular stiffness, and those which decrease endothelial responsiveness. The former are due, in large part, to histologic changes including an increase in the collagen and a decrease in the elastin components. The changes in collagen content are believed to be particularly marked in diabetics because of an increase in glycosylated collagen cross links associated with the disease. Increased central vascular stiffness increases the velocity of the pulse wave from the aortic valve to the iliac bifurcation and also the velocity of the reflected wave. This results in an increase in systolic, a decrease in diastolic, and therefore an increase in pulse pressure. From a clinical standpoint, this marker of central vascular stiffness has emerged as one of the most important risk factors for the development of cardiovascular disease in the middle-aged and older population. Data from the Framingham study indicate, in fact, that pulse pressure is a more important discriminator of cardiovascular risk than systolic or diastolic blood pressure. Increased vascular stiffness is also responsible for isolated systolic hypertension in older individuals. Surveys indicate that over half of older individuals with hypertension have an increase in systolic pressure associated with a normal or low diastolic pressure. Two large clinical trials indicate that treatment of isolated systolic hypertension in older individuals decreases stroke, heart failure, and infarction or cardiovascular death, particularly in older diabetic patients.

Increased vascular stiffness may also be responsible, in part, for the marked age-associated increase in mortality and morbidity following an infarction. Data from the GISSI-2 trial investigators, as well as other large infarction trials, demonstrate a logarithmic increase in in-hospital and 6-month mortality, as well as large increases in congestive heart failure and ventricular rupture as age increases from under 65 years to over 85 years. A report from the SAVE investigators indicates that increased vascular stiffness, indexed by pulse pressure, may be responsible, in part, for this age-associated rise in mortality. The third area where vascular stiffness may impact on cardiovascular disease is the development and progression of what is commonly termed diastolic heart failure in the elderly. Up to 40% of older individuals presenting with pulmonary edema may have a normal ejection fraction. Although symptoms are commonly attributed to a diastolic, relaxation abnormality, Hopkins data indicate that age-associated increases in both vascular and ventricular systolic stiffness may play an important role in many of these patients. In healthy individuals, interventions which decrease stiffness improve aerobic cardiovascular performance. Clinical trials are underway in patient populations as well.

The second major change in vascular properties associated with physiologic aging

is decreased endothelial responsiveness. This is demonstrated in coronary as well as brachial arteries, using both acetylcholine, and flow-mediated stimuli to assess endothelial function. The clinical implications of this change are profound, since endothelial dysfunction is believed to play a role in nearly every stage in the development, progression, and manifestation of atherosclerotic disease. Lipid lowering agents and ACE-inhibitors may achieve some of their striking clinical benefits, in part, by actions which improve endothelial responsiveness. An additional intervention currently under investigation is the administration of L-arginine, the substrate for nitric oxide synthase, which catalyzes the transformation of L-arginine to citrulline and nitric oxide, the substance which is believed to be defective and/or deficient in patients with endothelial dysfunction. L-arginine supplementation improves coronary artery responsiveness in short-term trials. Studies examining important clinical outcomes are underway in several patient populations.

In brief, the most important physiologic changes associated with vascular aging are increased central vascular stiffness and decreased endothelial responsiveness. From a clinical standpoint, these are important in understanding and treating older individuals with isolated systolic hypertension, acute myocardial infarction, and congestive heart failure, and may also play an important role in the development and progression of the basic atherosclerotic process. Recognition of these changes may stimulate the development and testing of new strategies directed to measuring and altering these changes and may also play a role in guiding the selection and dosing of existing therapies.

Consequences of vascular aging. Objectives:

to describe the physiologic changes associated with vascular aging in individuals without known atherosclerotic disease;

to review the manner in which these interact with common cardiovascular diseases in the elderly;

to discuss how recognition of these changes may influence the development of new therapies and guide the selection and dosing of existing therapeutic interventions.