Cardiovascular Aging

What We Can Learn
From Caloric Restriction*

Gary Gerstenblith, MD, FACC
Baltimore, Maryland

Cardiovascular aging is a universal phenomenon associated with an increased likelihood of the development of cardiovascular diseases and of adverse outcomes once disease does develop (1). In fact, most complications of cardiovascular disease, including myocardial infarction, stroke, congestive heart failure, atrial fibrillation, and cardiovascular death, occur in the increasing number and proportion of our population that is 65 years of age and older (2).

See page 398

Age-associated vascular changes include endothelial dysfunction and intimal proliferation, a recognized mechanism and substrate, respectively, for the development, progression, and manifestations of atherosclerotic disease; and increased central vascular stiffness, the most important etiology for isolated systolic hypertension in older persons. Age-associated changes in cardiac muscle include impaired early diastolic filling at rest and diminished performance during exercise and other stresses, manifested by decreased cardiac output, ejection fraction, and heart rate; and higher end-systolic and end-diastolic volumes. Increased vascular load and depressed cardiovascular performance contribute to impaired ventricular/vascular “coupling” during exercise (3). These age-associated changes increase the likelihood that the older patient will develop heart failure symptoms in the setting of a tachycardic, ischemic, or hypertensive insult that would not precipitate failure in the younger patient. Another important age-associated change is a decrease in the number and/or function of endothelial progenitor cells, which contribute to repair and/or regeneration of damaged vascular tissue (4,5). These cells may also transdifferentiate to form myocytes and aid in myocardial repair in the setting of ischemic or other injury (6).

Although aging is universal, it is not uniform. We observe in our everyday lives individuals of the same chronologic age whose mental and physical abilities markedly differ. In experimental models and humans as well, nearly all cardiovascular variables demonstrate a significant increase in heterogeneity with increasing age, with the result that cardiovascular performance of many older individuals is similar to that of others who are 20 or even 30 years younger than they are. Thus, chronologic age can be distinguished from cardiovascular age, and the term “successful” aging refers to individuals whose biological age is “younger” than their chronologic age. An additional term that is sometimes used to indicate biological age is “frailty,” which when used in general usually refers to physical limitations, but from a biological standpoint refers to a multi-organ process characterized by decreased reserve during stress, most importantly during the stress of illness, and increased time to recover homeostasis following stress (7).

The fact that aging is not just “a matter of time,” but varies among individuals, suggests that individual genetic backgrounds and/or environmental factors influence our expected lifespan at birth and/or the rate of aging. The accepted measure of factors influencing aging, per se, is maximal lifespan, defined as the mean survival of the longest-lived decile. Survival of this decile has not changed over time and is distinguished from the increase in average lifespan observed in the 20th century, owing primarily to more successful public health, preventive, and treatment interventions. The only environmental factor known to have a consistent effect on slowing the aging process in all studied experimental models is a caloric restriction diet (8). Decreasing caloric intake by 30% to 60% significantly prolongs maximal lifespan in laboratory animals when instituted at young or middle age. The effect does not depend on lower body weight, as there is no such prolongation when the same lower weight is achieved with exercise.

Evaluation of the relevance of the experimental findings to humans is sparse, in part because of the long time required to demonstrate a prolongation of maximal lifespan, uncertainty as to appropriate surrogate markers of aging processes, and the difficulty of following a calorie-restricted diet. Studies of Biosphere participants, for whom food availability was reduced for six months, and of individuals participating in the Caloric Restriction Optimal Nutrition Society for an average of six years demonstrated significant decreases in cardiovascular risk factors and C-reactive protein with caloric restriction (9,10).

The study by Meyer et al. (11) in this issue of the Journal adds significant information to our current knowledge concerning the effects of calorie restriction on cardiovascular aging. The investigators performed Doppler echocardiography and measured inflammatory markers in 25 individuals, the largest number reported to date, who were practicing caloric restriction for a mean of 6.5 years (range 3 to 15 years). Results were compared with those from 25 age- and gender-matched control individuals consuming a typical Western diet. The mean daily calorie consumption was 1,671 kcal in the caloric-restricted group, compared with 2,445 kcal in the control group. Daily salt intake was also significantly lower in the caloric-restricted group (a mean of
2.6 g/day vs. 3.4 g/day). Mean body mass index was 19.7 kg/m² in the caloric-restricted group compared with 27.0 in the control group, and mean systolic and diastolic pressures were also significantly lower in the caloric-restricted (102 ± 10 mm Hg and 61 ± 7 mm Hg) compared with the control group (131 ± 11 mm Hg and 83 ± 6 mm Hg). There was no difference in systolic function as assessed by left ventricular fractional shortening in the two groups, which is consistent with cross-sectional studies demonstrating no age effect on resting systolic function. However, measures of diastolic function, including the ratio of peak E-wave to peak A-wave, deceleration time, and velocity assessed at the mitral annulus during early left ventricular filling all demonstrated significantly “younger” values in the calorie-restricted group. In addition, mean high-sensitivity C-reactive protein (0.3 ± 0.3 mg/l vs. 1.9 ± 2.8 mg/l) and tumor necrosis factor alpha (0.8 ± 0.5 pg/ml vs. 1.5 ± 1.0 pg/ml) were both significantly lower in the caloric-restricted group.

The study is the first to describe the effects of caloric restriction on a well-recognized marker of cardiovascular aging in humans. It also highlights the role of inflammation as a potential responsible mechanism. There are limitations inherent in the study design, some of which the authors note. The study was not randomized, limiting conclusions regarding causation. It is probably not possible to perform a randomized study of the required duration with caloric restriction unless, perhaps, new appetite-suppressant drugs are developed. Meaningful correlations between the inflammatory and cardiovascular variables probably require a larger sample size. It also may not be possible, without studying additional individuals, to determine whether the improved diastolic function was mediated in part or entirely by the lower blood pressures and whether the lower C-reactive protein was related to the lower body mass index.

It is anticipated that this study will stimulate additional work in the area, including longitudinal analyses in the same individuals to determine whether the “trajectory” of aging is indeed slower with caloric restriction. In rodent models, caloric restriction also delays or prevents the development of cataracts, diabetes, cancer, and autoimmune diseases (8), and it is hoped that studies of these outcomes will also be performed in the volunteers. Experimental models also indicate that caloric restriction is associated with a significant decrease in oxidative stress, probably by decreasing metabolic rate, and this would also be useful to study in humans (12). Although the likelihood that most individuals would adopt such an intervention is small, the value of the study is that it points to possible mechanisms explaining how aging occurs and, therefore, how it may be modified. The authors, and the disciplined volunteers following the practice of caloric restriction, are to be congratulated for their important contributions to this effort.

Reprint requests and correspondence: Dr. Gary Gerstenblith, Carnegie 591, Johns Hopkins Hospital, 600 North Wolfe Street, Baltimore, Maryland 21287. E-mail: gblith@jhmi.edu.

REFERENCES