The Aging Human Heart

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There seems to be more about aging than living longer.1,2 Certainly, among most humans, longevity is determined by exposure to environmental risk factors that account for morbidity and eventual mortality.3 However, it is not known whether control for most or all environmental risk factors would assure humans unlimited survival. The concept that among members of our species, survival is predetermined biologically remains to be disproven.4 Worldwide, cardiovascular aging is of great importance to gaining greater insight into cardiovascular aging.8

The advent of noninvasive technologies that allowed for the direct assessment of global systolic function in humans to the important realization that, contrary to what one might intuitively expect, left ventricular (LV) ejection fraction did not decline with aging, particularly when obstructive coronary artery disease was excluded or accounted for in longitudinal cohorts.8 More recent work indicated in fact that the human heart remodels significantly with aging,7 while the LV ejection fraction remains at normal levels. The mechanisms of age-related cardiac remodeling remain incompletely understood, but how and why the aging heart remodels the way it does is of great importance to gaining greater insight into cardiovascular aging.

In this issue of Circulation: Cardiovascular Imaging, Hung et al10 document important findings on human cardiac aging. They demonstrate that advanced aging is associated with greater LV concentricity expressed as the ratio of LV mass to volume at end diastole, impaired relaxation with reduced filling, impaired longitudinal deformation with preserved circumferential shortening, and greater torque, that is, shear in the longitudinal–circular orientation.16 Conversely, it is possible that deformation in the circumferential–radial plane is so essential to LV function that remains preserved by torque and other mechanisms in the face of longitudinal shortening impairment. Along a similar line of thinking, it is conceivable that systolic function expressed by LV ejection fraction or myocardial systolic strain indices would be altered only at more advanced stages of subclinical involvement. However, diastolic function might be impaired earlier in a disease progression continuum since it is not as pivotal as systolic function. Conversely, among the limitations of such type of thinking is the impressive reduction of stroke volume documented by this and previous work in association with concentric remodeling and diastolic dysfunction. This could reflect independent pathways of cardiovascular impairment because of systolic versus diastolic dysfunction, which could be sex related.8,9 Finally, from a mechanical standpoint, the work by Hung et al8 reminds us once again of the limitations of ejection fraction as an index of LV function across the human lifetime. Recent work points to the advantages of integrating structure and function to better express the effects of continued risk factor exposure over prolonged periods of time.37

The main limitation of the work by Hung et al8 is acknowledged by the authors and relates to the study design which derives longitudinal inferences from cross-sectional relationships obtained from the ARIC study (Atherosclerosis Risk in Communities). Although the importance of cohort effects cannot be underestimated, in the case of this specific study, at least 3 of the main parameters have been studied in longitudinal

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studies involving individuals of similar age range enrolled in MESA (Multiethnic Study of Atherosclerosis), in analyses that also excluded participants with prevalent heart failure, providing, therefore, a frame for comparison with the results reported by Hung et al. As previously reported by Eng et al, LV mass increased in men but not in women over a period of 10 years but only by a small amount of in average 3 to 6 g. By contrast, LV end-diastolic volume decreased both in men and in women, and concentric remodeling expressed as the LV mass to volume ratio increased markedly with aging. Based on those results, findings of increased concentric remodeling reported by Hung et al seem to be well supported by magnetic resonance imaging–determined LV mass and volume measurements performed longitudinally. Similarly, longitudinal measurements of circumferential shortening performed in MESA using magnetic resonance imaging tagging support the findings of Hung et al in ARIC using echocardiography.

The mechanisms underlying the age-related remodeling reported by Hung et al and others remain incompletely understood. Age-related LV hypertrophy, now thought to be primarily concentric, seems to be in part secondary to progressive systolic and pulse pressure increases combined with diastolic blood pressure reduction. These cardiac remodeling alterations are in part attributed to increased arterial stiffness associated with the aforementioned blood pressure changes, as well as changes in body mass and composition that also accompany human aging in industrialized societies. Numerous other factors underlie myocyte hypertrophy due mostly to in series sarcomere growth as the heart ages, and its susceptibility to sex hormonal modulation has been proposed as one of the main mechanism of sex differences in age-related LV remodeling and myocardial dysfunction as discussed by Hung et al. A myriad of additional factors have been reported in association with cardiac aging and several have been postulated as primary or contributing determinants of cardiac remodeling, including age-related apoptosis, metabolic dysregulation associated with activation of the renin–angiotensin system, chronotropic alterations related to aging of the autonomic nervous system, mitochondrial abnormalities, and many others. Among them, the potential influence of myocardial fibrosis has received particular attention, given that fibrosis plays a pivotal role in vascular aging.

Myocardial replacement fibrosis with scar formation is primarily secondary to coronary artery disease and hypertensive heart disease in population studies. It is more common in men than in women and associated with LV dilatation and eccentric remodeling in those studies. Conversely, interstitial fibrosis is more common in women in population studies and also associated with LV hypertrophy but not with specific markers of coronary artery disease, such as coronary calcification defined by computed tomography. Venkatesh et al have reported the association of interstitial fibrosis with LV size reduction, a central component of the aging-related concentric remodeling reported here by Hung et al and by prior work. Moreover, Donekal et al reported associations of interstitial fibrosis with both diastolic dysfunction and increased torque among women and between interstitial fibrosis and regional systolic dysfunction among women and men even after participants with replacement fibrosis were excluded from the analysis.

Taken together, such findings suggest a potential role for myocardial interstitial fibrosis as a mechanism for alterations reported by Hung et al.

Finally, Hung et al demonstrate the feasibility of using 3D echocardiography in over a thousand participants of a large population study to study myocardial mechanics, in addition to global indices of myocardial structure and function, such as LV mass, volumes, stroke volume, and ejection fraction. Does this herald the future substitution of 2D by 3D echocardiography as the main tool to assess cardiac function in clinical investigation and clinical practice? In this regard, the main limitations of 2D echocardiography and planar ultrasound imaging in general relate to operator dependence and impaired reproducibility because of the difficult registration of 2D planes in 3D space. Although current 3D echocardiography techniques still have limited versatility, the demonstration of a detailed mechanical analysis in a large population study does announce the possibility that faster and more powerful computing technology could, in a not so distant future, bring 3D echocardiography to the forefront of quantitative imaging not only in clinical investigation but also in clinical practice. In this direction, the work by Hung et al represent an important milestone.

In summary, cardiac remodeling, as demonstrated by Hung et al, is characterized by concentric remodeling, reduced stroke volume, and maintained ejection fraction. Mechanically, although longitudinal shortening declines with aging, ventricular torque increases, particularly among women, to apparently compensate for reduced shortening and maintain the ejection fraction. These changes are likely secondary to lifetime exposures to established as well less well characterized cardiovascular or novel risk factors, but could also result from predetermined biological mechanisms that intrinsically limit longevity in humans.
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