Cardiac Senescence, Heart Failure, and Frailty: A Triangle in Elderly People

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Cardiovascular disease (CVD) is a common problem in the elderly. In particular, the morbidity and mortality of patients with heart failure (HF) increase with age. The poor outcomes of elderly patients with HF can be explained partly by cardiac aging at the cellular and organ levels. Moreover, recent evidence has demonstrated that functional evaluation, which may reflect the status of individual aging, predicts mortality in patients with HF. Age-related changes occur throughout the body and in virtually all organ systems. Thus, we should pay more attention to geriatric conditions when treating patients with HF. Frailty represents a complex clinical syndrome that results from multiple impairments across different organs and is characterized by decreased physiological reserves and increased vulnerability to stressors. Frail patients with CVD have a worse prognosis than non-frail patients. Evidence demonstrates that frailty is an independent risk factor for incident HF among older people. The ways in which cellular senescence promotes age-related CVD and frailty remain an important issue in the biology of aging and clinical geriatrics. Senescent cells that have acquired a senescence-associated secretory phenotype (SASP) can cause local and potentially systemic inflammation. SASP might be a key phenomenon in the association between cellular senescence and the development of age-related CVD and frailty. Frailty is a dynamic and potentially reversible state; therefore, translational research efforts are focused on obtaining mechanistic insights into the pathobiology of frailty, the development of novel therapeutics, and the identification of biomarkers for frailty. This is particularly important in developed countries that are confronted with an aging society. (doi: 10.2302/kjm.2015-0015-IR)

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Increased Prevalence of HF with Age

The process of age-associated tissue deterioration leads to a decrease in the overall health of aging populations. Although the biology of aging is not well understood, CVD is a common problem in the elderly.1,2 For example, left ventricular (LV) hypertrophy, atrial fibrillation, and coronary arteriosclerosis are fundamental cardiovascular problems for which the risks increase dramatically with age.1,2 Consequently, the incidence of myocardial infarction (MI) increases with age.3 Clinical evidence demonstrates an age-related increase in the rate of cardiac rupture after MI and an increase in both in-hospital and post-discharge mortality rates.3 Even though a patient might avoid early death after MI, HF might occur in later years because MI is the most common cause of HF associated with systolic dysfunction. It is important to note that approximately half of older patients with HF have normal LV systolic function but abnormal LV diastolic function. The prognosis of HF is similar for patients with...
LV diastolic dysfunction and LV systolic dysfunction.\(^4\) In addition to the high incidence of HF in older people, the high mortality rates and associated costs make HF one of the most clinically challenging chronic diseases to treat.\(^5,6\)

The poor outcomes of HF in the elderly can be explained, at least in part, by cardiac senescence at the cellular and organ levels.\(^7\) Moreover, recent evidence has demonstrated that functional evaluation, which may reflect the status of individual aging, predicts mortality in patients with HF.\(^5,8–11\) This suggests the existence of a specific interaction between cell-autonomous and non-cell-autonomous mechanisms of the aging process. Therefore, better understanding of both individual and organ aging is needed to develop novel therapeutics for the clinical management of older patients with HF. This is particularly important in developed countries that are confronted with an aging society, thanks in part to progress in medical care that has improved the quality of life and lengthened the average lifespan.

**Cardiac Senescence at the Organ Level**

The heart exhibits a continuum of structural and functional alterations during the aging process. These age-associated alterations are most likely related to the sharp increase in the incidence of LV hypertrophy, atrial fibrillation, and HF observed in the elderly population.\(^2\)

**1) Structural Changes**

In cross-sectional studies of patients without hypertension or clinically apparent CVD, LV wall thickness increases with age in both sexes.\(^2\) Elderly patients without apparent CVD do not have an overall increase in LV mass at autopsy; however, compared with younger patients, elderly patients have cardiomyocyte enlargement associated with a robust decrease in the estimated cardiomyocyte number.\(^2\) Increased collagen is observed in the aged myocardium in association with increased formation of collagen cross-linking. In addition, waste metabolites accumulate in the aged myocardium. Molecules such as lipofuscin, a brown granular pigment that consists of cross-linked lipids and proteins produced during lysosomal digestion, and amyloid, aggregates of insoluble fibrous protein, are evident in the aged myocardium.\(^7\)

**2) Functional Changes**

LV systolic performance at rest is preserved during aging without apparent CVD.\(^2\) However, the maximum ejection fraction during exhaustive upright exercise decreases with age in healthy subjects. This age-associated decrease may be explained by a decrease in coronary flow reserve as a result of coronary arteriosclerosis and the impaired response of contractile function and heart rate to \(\beta\)-adrenergic stimulation during exercise in the elderly.

Impaired LV diastolic function in the elderly also might contribute to the decline in the maximal cardiac performance during exercise. In contrast to systolic LV function, LV diastolic performance is predominantly altered with aging.\(^2,4,7,12\) Echocardiographic evaluations confirm an age-associated reduction in early diastolic filling rate and an increased late filling of the LV in the human heart.\(^2\) Senescent cardiomyocytes are characterized by prolonged relaxation, diminished contraction velocity, a decrease in \(\beta\)-adrenergic response, and increased myocardial stiffness.\(^2\) This impairment in LV diastolic function contributes to the increased incidence of HF and atrial fibrillation in the elderly.\(^2\) Evidence from studies using senescent rodents demonstrates slowed relaxation and altered \(\text{Ca}^{2+}\) handling in isolated cardiomyocytes.\(^2,13\) In particular, impaired sarcoplasmic reticulum \(\text{Ca}^{2+}\)-ATPase activity, which is mainly responsible for controlling intracellular \(\text{Ca}^{2+}\) concentration by regulating uptake of \(\text{Ca}^{2+}\) into the sarcoplasmic reticulum during relaxation, has been shown to contribute to abnormalities in cardiac relaxation.\(^14\) These phenomena are also observed in the senescent human myocardium.\(^15\)

In addition, the accumulation of myocardial collagen and extracellular matrix increases with age, contributing to myocardial stiffness and cardiac diastolic dysfunction.\(^2\) Furthermore, the increase in size of cardiomyocytes contributes to age-associated diastolic dysfunction. Cardiomyocyte hypertrophy is associated with changes in cytoskeletal proteins that could alter the microtubule architecture and heighten the organization of sarcomeres within individual myocytes. Increased collagen volume fraction, larger cardiomyocyte diameter, and higher resting cardiomyocyte tension are all correlated with LV diastolic stiffness.\(^2\) Posttranslational modification of myofilament proteins such as titin may also play an important role in age-associated LV diastolic dysfunction.\(^7\)

**Cardiac Senescence at the Cellular Level**

Cardiac senescence can be characterized by both quantitative alterations, e.g., a decrease in the number of cardiomyocytes with age\(^2,16\) and qualitative alterations, e.g., changes in cardiomyocyte properties and extracellular matrix with age.

The number of cardiomyocytes is determined based on the balance between cardiomyocyte death and the renewal of cardiomyocytes, both of which are greatly influenced by age.\(^7\) Quantitative changes that occur with aging include cardiomyocyte hypertrophy and autophagy. Because most cardiomyocytes do not divide and because their higher energy requirements expose the cells to a high level of accumulated oxidative damage, autophagy is essential for cardiomyocytes to maintain their long-term function and survival.\(^3,17,18\) Despite the increased need for autophagy to eliminate dysfunctional cellular
components, aging is associated with reduced efficiency of autophagy. Failure to eliminate dysfunctional mitochondria by autophagy could lead to further accumulation of oxidative damage and induction of apoptosis by the release of cytochrome \( c \) from impaired mitochondria. Although the mechanisms involved in impairment of autophagy in the aged heart are not well understood, intralysosomal accumulation of lipofuscin is likely involved. Lipofuscin is associated with modification of proteins and lipids by reactive oxygen species (ROS) and is responsible, at least in part, for the gradual inhibition of autophagy with aging.

Cardiomyocyte hypertrophy is pronounced in the aged heart and contributes to the development of a dysfunctional heart. Increased protein synthesis in response to hypertrophic signaling under inefficient autophagy and cytosolic saturation of oxidative damage causes the accumulation of damaged proteins and organelles. In addition, hypertrophic cardiomyocytes have increased energy demands and thus require a greater production of energy by the pool of dysfunctional mitochondria. Subsequently, ROS production from dysfunctional mitochondria further increases, and the subsequent release of cytochrome \( c \) leads to cardiomyocyte apoptosis.

Cardiac senescence occurs not only in cardiomyocytes but also in non-cardiomyocyte cells. Although cardiomyocytes are the main functional units of the heart, non-cardiomyocytes constitute more than half of the cells in the heart. Cardiac fibroblasts provide the cardiac scaffold through the production, maintenance, and remodeling of extracellular matrix. Fibroblasts obtained from aged hearts have impaired proliferative capacity and do not respond to profibrotic stimuli in vitro. Aged hearts subjected to MI exhibited reduced collagen deposition in the scar, delayed stabilization of scarring, and reduced but prolonged inflammation, suggesting that cardiac fibroblasts become dysfunctional with aging. This dysfunction may contribute to the increased risk of cardiac rupture following MI in the elderly. In addition to the cellular changes associated with aging, the extracellular matrix also undergoes age-related changes. These cellular and molecular alterations affect cardiac function during the aging process and most likely contribute to the higher incidence of CVD in the aging population.

Frailty as the Status in Which Individual Aging Is Accelerated

Because of the increasing age of individuals with HF, age-specific approaches to treatment are urgently required. Age-related changes occur throughout the body and in virtually all organ systems. Consequently, we should pay more attention to common geriatric conditions such as poor mobility, multiple disabilities, malnutrition, and cognitive impairment. Each of these conditions significantly affects the course of HF, its management, and its prognosis in the elderly.

Frailty represents a complex of clinical syndromes characterized by decreased physiological reserves and increased vulnerability to stressors as a result of multiple impairments across different organs. Stressors are widely classified as acute illness, chronic illness, or iatrogenic factors. When exposed to such stressors, frail patients are at risk for disproportionate decompensation, adverse events, procedural complications, prolonged recovery, functional decline, disability, and mortality. Frailty has multiple contributors, including the age-associated loss of skeletal muscle mass, reduced nutritional intake, and low physical activity in addition to CVD and non-cardiovascular chronic diseases such as chronic obstructive pulmonary disease, chronic kidney disease, and type 2 diabetes mellitus. More recently, neuropsychiatric status, including cognitive impairment and depression, and social conditions such as loneliness have been shown to contribute to frailty. Although frailty is widely recognized in the health care literature, the concept of frailty lacked a formally accepted definition until recently. A consensus group consisting of delegates from international, European, and American societies defined frailty as “a medical syndrome with multiple causes and contributors that is characterized by diminished strength, endurance and reduced physiologic function that increases an individual’s vulnerability for developing increased dependency and/or death.”

Tools for Identifying Frailty

Numerous tools to measure frailty have been developed. They can be divided into two groups: the phenotype model and the accumulation of deficits model, as represented by the Fried Frailty Scale and the Frailty Index, respectively. The Fried Frailty Scale, which was proposed in 2001 by Fried et al., is frequently used in the clinical setting. In a secondary analysis of the Cardiovascular Health Study, Fried established a frailty phenotype based on five criteria: unintentional weight loss, self-reported exhaustion, low physical activity, slow walking speed, and weakness. Patients meeting more than three of these criteria were categorized as frail, and those meeting one or two criteria as pre-frail. In this analysis, there was a graded association between frailty status and adverse health outcomes, including mortality. However, whether the time-intensive nature of the Fried Frailty Scale is useful in clinical practice and whether single-measure assessments such as the 5-m walking speed or handgrip strength are sufficient to identify frailty remain controversial. Other examples of the phenotype approach include the Short Performance Battery (SPB) and the Gill Index. The SPB is a group of measures combining walking speed, chair stand, and balance tests. The Gill Index is also based on a composite of chair stand and walking speed tests. These scores incorporate the measurement of...
mobility and the ability to perform the activities of daily living (ADL).

Frailty is also assessed as a multidimensional accumulation of deficits, as opposed to a single clinical phenotype. This approach is well represented by the Frailty Index (which was developed as a part of the Canadian Study of Health and Aging) wherein 92 baseline variables consisting of signs, symptoms, disability, and laboratory values are used to define frailty.28,29 There is a significant association between the accumulation of deficits and chronological aging. The index is calculated as the ratio of deficits present to the total number of variables assessed. A higher index is strongly linked to increased risk of death and institutionalization independent of chronological age.30 Finally, the Frailty Index can be simplified to a 30-item bedside assessment tool without loss of predictive validity.31 The accumulation of deficits approach also includes the following scoring systems: Changes in Health, End-stage Disease and Signs and Symptoms; the MacArthur Study of Successful Aging; and the Resident Assessment Instrument.5 These scoring systems can examine the whole domain of deficits, including impairment, disability, and comorbidities, in contrast to the phenotype model.

**Pathobiology of Frailty**

The pathobiology of frailty is a field of ongoing research and debate.32 In addition, the way in which cellular senescence promotes age-related CVD and frailty remains an important issue in the biology of aging and clinical geriatrics. Senescent cells that have acquired a SASP can cause local and potentially systemic inflammation by secreting inflammatory cytokines.33 Thus, SASP might be a key phenomenon in the association between cellular senescence and the development of age-related CVD and frailty. The putative mechanisms of frailty include dysfunction of the immune, hormonal, and endocrine systems32,34 (Fig. 2). Specifically, upregulation of inflammatory cytokines such as interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor-α (TNF-α); decreased androgen levels; increased growth hormone (GH) levels and decreased insulin-like growth factor-1 (IGF-1) levels; and insulin resistance are frequently observed in frail patients.8,10,32,34 These phenomena lead to an anabolic–catabolic imbalance in which muscle breakdown exceeds muscle synthesis, resulting in a progressive decline in muscle mass and muscle strength, known as sarcopenia.35 Under stressed conditions, subclinical impairments are unmasked and a vicious cycle of physical inactivity and malnutrition develops, leading to further decline in individual’s ADL levels.32,34

![Fig. 1 Trajectories of health and functional decline with aging.](image-url)
Primary Frailty and Secondary Frailty Associated with HF

Complicating the literature on frailty is the number of working definitions for seemingly similar processes with respect to both primary frailty caused by aging and secondary frailty associated with comorbidities (Fig. 2). For example, the pathobiologies of frailty and HF share several common pathways, particularly a consistent correlation with inflammatory biomarkers such as IL-6, CRP, and TNF-α.6,8,10 In addition, immune cells and cytokines, which are known to exert detrimental effects on the arterial wall by promoting atherosclerosis and vascular senescence, also accelerate the aging process and impact body composition, thereby promoting frailty.6,8,10 Even during the subclinical phase, HF contributes to the development of frailty by causing impairment in multi-organ systems.36 The wasting process of HF is most likely related to an anabolic–catabolic imbalance in which adaptive neurohormonal mechanisms and autonomic nervous activation during the initial phase yield detrimental effects in the long term.10 In addition to the upregulation of inflammatory cytokines, abnormalities in the GH/IGF-1 axis, cortisol regulation, and insulin resistance are frequently observed in HF-related frailty.10 This biological link frames the epidemiological data demonstrating that frailty and HF coexist in a large number of individuals.10,11,37

Although patients with symptomatic HF often have cellular and molecular alterations in muscle cell composition, these changes slightly differ from those of normal aging and inflammatory processes.10 The changes in skeletal muscle in patients with HF are complex and site-specific and are similar to a mixture of chronic deconditioning and inflammation.10 However, the specific relationship between these muscle changes and HF-related frailty has yet to be fully clarified. Thus, further experimental and clinical studies to elucidate the molecular and cellular etiology of HF-related frailty, as distinct from primary frailty, will have implications for prevention, treatment, and reversibility of HF-related frailty.

Current Status of Evidence

A systematic review of 21 studies estimated the prevalence of frailty in community-dwellers older than 65 years to be 10% for physical frailty and 14% for a broader frailty phenotype.38 In general, the prevalence of frailty increases with age, and is higher in women and residents of long-term care facilities.25,39 The prevalence of frailty ranges from 10% to 60% in elderly patients with CVD, depending on the population studied and the frailty assessment tools used.6,8,11,37,40 Frail patients with CVD have a worse prognosis than non-frail patients.6,8,11,40

Fig. 2 Two distinct pathways toward the phenotype of frailty.
Frailty is particularly common in patients undergoing transcatheter aortic valve replacement. It is also common among patients with HF (the prevalence ranges from 15% to 74%) because the pathophysiology of HF directly contributes to frailty by reducing exercise capacity and skeletal muscle function. Furthermore, patients with HF are more susceptible to falls and cognitive impairment because of reduced cerebral perfusion, which accelerates the development of frailty and disability. Thus, frailty is a strong predictor of mortality, rehospitalization, and impaired quality of life in patients with chronic HF. In patients with decompensated HF who are admitted to the hospital, simple measurements of physical function have been associated with the length of hospital stay, reduced ADL, higher readmissions, and mortality.

In contrast, increasing evidence demonstrates that frailty is an independent risk factor for incident HF among older people. In the Cardiovascular Health Study, the prevalence of HF was 8 times higher in frail patients than in non-frail patients. Frailty might predispose to myocardial damage by reducing resistance to stressors such as myocardial ischemia, pressure and volume overload, and arrhythmias, subsequently leading to decompensation and hospitalization.

**What Should Be the Next Focus of Research?**

Frailty is a dynamic and potentially reversible state. Adverse outcomes in frail patients would be reduced by optimal treatment of the presenting CVD and comorbidities.Polypharmacy is an essential issue in the management of frail patients with HF. Unfortunately, current evidence-based medicine guidelines do not usually account for frailty and other overall health care issues in the elderly. Therefore, we should develop the optimal care for older patients with CVD by performing an objective assessment of frailty (Fig. 3). It is also important to identify the causes of frailty and their association with comorbidities because comorbidity-related frailty (secondary frailty) is relatively easily reversed with appropriate treatment. Frailty is recognized to be intrinsic and less likely to improve when the degree of frailty is disproportionate to the burden of comorbidity. To improve the reversibility of primary frailty, current translational research efforts are focused on obtaining mechanistic insights into the pathobiology of frailty, promoting the development of novel therapeutics, and identifying biomarkers for frailty. Current treatments for frailty include exercise (resistance and aerobic), caloric and protein support, and vitamin D supplementation. It might be useful to incorporate androgen treatment or caloric restriction mimicry into the clinical management of frail patients. In addition,
targeted therapy to immune cells that are responsible for the development of immunosenescence may be promising. Such attempts will be achieved for the first time by combining our knowledge of cardiology and geriatrics (including aging science). Because I have been studying geriatric cardiology for many years, I gain much satisfaction and enjoyment in observing the growing recognition of the importance of this field, one that I have long considered to be of great importance.

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