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Frailty

*Keystone in the Bridge
between Geriatrics and Cardiology*

William Russell Hazzard, MD

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The 20th century witnessed an historical change in the landscape of human evolution as the limits of human longevity pressed ever upward in advanced cultures. At the outset of the 20th century, average longevity in America barely exceeded 48 years and only 3% of the population was over the age of 65. This reflected the underdeveloped status of our nation at that time, when public health measures were minimal, nutrition, hygiene,

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housing, and sanitation precarious, antibiotics unknown, childhood deaths from infectious diseases were frequent, and death from chronic diseases in old age uncommon. However, by the end of 20th century the picture had changed dramatically. Average American longevity exceeded 75 years, childhood deaths had declined precipitously, and survival to middle and even old age had become the norm. Now early in the 21st century, American society and the American health care system in particular is at a crossroads between opportunity and crisis: on the one hand, the prospect of extending average human longevity to its maximum draws near (85 ± 7 years has been suggested as our “barrier to immortality” [1]); on the other hand, the physician’s image of their typical patient 85 or older raises the specter of an impending epidemic of sick, vulnerable, and disabled old people, frail patients who will require extraordinary levels of health and social care. This looms as a defining feature of the 21st century as members of the current wave of Americans born in the post-World War II era approach old age over the next half century: will American society become overwhelmed by the needs of aged, frail, and dependent “baby-boomers” in gradual decline, or will effective preventative public health and medical interventions succeed in prolonging their robust health and independence into advanced old age, ideally compressing their illnesses and dependency into a brief period before death?

Nowhere is the urgency to resolve this approaching dilemma more pressing than in the field of cardiovascular disease (CVD). CVD as the primary cause of death accounts for nearly half (approximately 46%) of deaths throughout middle and old age, cardiac deaths rising logarithmically with age in parallel with all-cause mortality. The prospect of facing a tsunami of aging baby-boomers who develop CVD and disability in their 70s, 80s, and 90s has spawned a new subfield, geriatric cardiology (the central subject of this entire volume). Here, as in all subspecialties of adult medicine, the special nuances of geriatrics have emerged as a focus for cardiology as it struggles to prepare for the impending surge of elderly patients in their domain.

A phenomenon of special interest to geriatricians and cardiologists (and geriatric cardiologists in particular) is the syndrome of frailty. This condition is highly prevalent among the elderly, especially the “oldest old” (those above 85). Yet it remains but vaguely defined and is often mistakenly applied interchangeably with co-morbidity and disability. This chapter is designed to persuade the critical reader that careful consideration of this syndrome as increasingly better characterized and investigated perhaps best captures the essence of the field of geriatrics and notably geriatric cardiology. Thus, systematic, serious, and critical research on the definition, diagnosis, pathophysiology, prevention, presen-

tation, and management of this syndrome should advance the characterization of frailty well beyond its long-time status as, “You know when you see it,” and the fatalistic, even nihilistic attitude that such dismissive assignment invites.

FRAILITY: THE DEFINITION EMERGING FROM EPIDEMIOLOGY

The fields of geriatrics and chronic disease management have long struggled for a meaningful definition of “frailty” and the related condition “failure to thrive.” This phenomenon is the subject of an elegant chapter by Linda Fried and Jeremy Walston in the recent, fifth edition of the *Principles of Geriatric Medicine and Gerontology* (2). These authors suggest that frailty and failure to thrive “represent a continuum of a clinical syndrome, with Failure to Thrive being the most extreme manifestation that is associated with a low rate of recovery and presages death.” In their treatise, they detail the definition and the pathophysiology of frailty, carefully dissecting its component parts before reintegrating them into a construct that comprises a complex web of the pathogenesis and clinical manifestation of this syndrome (Fig. 1).

The scientific underpinning for their definition of this syndrome has been strengthened by a series of publications from the Cardiovascular Health Study (CHS) from which the definition of frailty is largely derived (3). This was a prospective, observational, community-based epidemiological study of men and women 65 years of age or older in four US communities: Sacramento County, California; Washington County, Maryland; Forsyth County, North Carolina; Allegheny County, Pennsylvania ($N = 5201$). This was initiated in 1989–1990, with an additional cohort of 687 African-American men and women recruited in 1992–1993 from three of these sites. Participants were recruited from age- and gender-stratified samples from the Health Care Financing Administration Medicare eligibility lists in those counties. Both cohorts received identical baseline evaluations (except for the absence of spirometry and echocardiogram at baseline in the latter cohort) and follow-up with annual in-person examinations and semi-annual telephone calls for surveillance of outcomes, including disease, hospitalization, falls, disability, and mortality.

Baseline evaluations included standardized interviews that ascertained demographics, self-assessed health, health habits, weight loss, medications used, and self-reported physician-diagnosed CVD, emphysema, asthma, diabetes, arthritis, renal disease, cancer, and hearing and visual impairment. Leisure-time activities were determined by administration of a version of the Minnesota Leisure Time Activities Questionnaire cover-

ing the 2 weeks prior to study involvement. Physical function was assessed by asking about difficulty with 15 tasks of daily life, including mobility, upper extremity function, instrumental activities of daily living (IADL) and activities of daily living (ADL). Frequency of falls during the prior 6 months was assessed by self-report. The modified 10-item Center for Epidemiological Study–Depression scale (CES–D) was used to ascertain depressive symptoms.

The presence of significant co-morbidities was also determined. These included cardiovascular diseases (myocardial infarction [MI], congestive heart failure [CHF], angina, peripheral vascular disease, and stroke). The presence of co-morbidities was validated by medications used and through standardized examinations, including echocardiogram, and the posterior tibial/brachial artery systolic (ankle-arm) blood pressure (BP) ratio. Medical records were reviewed by clinicians for consensus-based adjudication based on standardized algorithms. Other examinations measured weight, BP, maximal stenosis of internal and common carotid arteries by carotid ultrasound, and fasting blood analyses for glucose, albumin, creatinine, and fibrinogen, plus lipid analyses, with low-density lipoprotein (LDL) cholesterol estimated by calculation from total and high-density lipoprotein (HDL) cholesterol and triglyceride levels. Additional serum samples were stored for future analyses, which have notably included C-reactive protein (CRP). Cognitive function was assessed with Mini-Mental State Examination (MMSE) and the digit symbol substitution test. Standardized performance-based measures of physical function included time (in seconds) to walk 15 feet at usual pace and maximal grip strength (in kilograms) in the dominant hand using a hand-held dynamometer.

For this study, the investigators defined frailty as “a biologic syndrome of decreased reserve and resistance to stressors resulting from a cumulative decline across multiple physiologic systems, and causing vulnerability to adverse outcomes.” They operationalized this definition of a frailty phenotype in the CHS according to the following criteria:

1. Shrinking: unintentional weight loss, of 10 pounds or more in the past year or, at follow-up, of at least 5% of body weight in the prior year (by direct measurement).
2. Weakness: grip strength in the lowest 20% (quintile) at baseline, adjusted for gender and body mass index.
3. Poor endurance and energy: as indicated by self-report of exhaustion, identified by two questions from the CES-D scale and associated staged exercise testing as indicator of VO_2 max.
4. Slowness: the slowest quintile of the study population, based on time to walk 15 feet, adjusting for gender and standing height.

5. Low physical activity: a weighted score of kilocalories expended per week, based on each participant's self-report, in the lowest quintile of physical activities specific to gender.

In this study, frailty was defined by the presence of three or more of these criteria. "Pre-frailty" was assigned to those participants with one or two of these attributes.

Because of possible confounding, subjects were excluded from the data analysis if they were significantly demented (with an MMSE of 18 or less) or were taking sinemet, donazepil, or antidepressants.

The 5317 people evaluated ranged from 65 to 100 years of age; 58% were female; 15% were African-American. At baseline, 7% of the cohort qualified for assignment of the frailty phenotype, 47% were pre-frail, and 46% met none of the five criteria. The prevalence of frailty increased with each advancing 5-year age group and was up to twofold higher for women than men, especially below age 80. African-Americans, especially women, had twice the prevalence of frailty as their non-African-American counterparts.

Analyses by Cox proportional hazard model models assessed the independent contribution of baseline status to major outcomes occurring over 3 and 7 years (for the two cohorts), specifically including incident frailty (including conversion from pre-frailty), falls, worsening mobility, ADL function, hospitalization, and death. Covariates were selected based on analysis of the first cohort. External validation using the second cohort showed agreement with results from the first.

In the first cohort, the 3-year incidence of frailty was 7%, with an additional 7% for the following 4 years. The second cohort (of African-American) had a 4-year frailty incidence rate of 11%. Other covariates of frailty included lower education, lower income, poorer health, and higher rates of co-morbid chronic diseases and disability. Specifically, those who became frail had significantly higher rates of CVD and pulmonary disease, arthritis, and diabetes, whereas there was no significant difference in cancer between those who became frail and those who did not. Both lower cognition and greater depressive symptomatology were associated with frailty (even after exclusion of those with MMSE <18 or who were on antidepressants at baseline).

At baseline, there was also a strong association between the frailty phenotype and self-reported disability, which was present in 76%: 72% reported difficulty in mobility tasks; 60% had difficulty with IADLs, whereas only 27% of those had difficulty in ADLs. Increasing disability paralleled increasing frailty in stepwise fashion. Viewed from a different perspective, however, among those with difficulty with ADLs, only

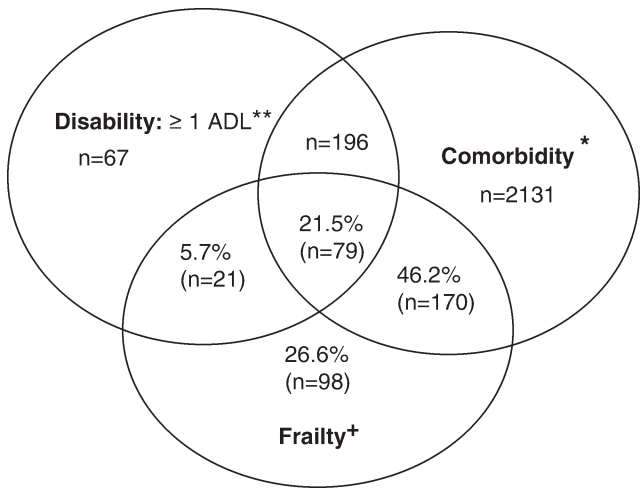


Fig. 2. Venn diagram of the relationships among frailty, disability (in activities of daily living [ADL]), and comorbidity (two or more diseases; myocardial infarction, angina, congestive heart failure, claudication, arthritis, cancer, diabetes, hypertension, chronic obstructive pulmonary disorder) in 2762 subjects in the Cardiovascular Health Study (CHS). (From ref. 3. Copyright © The Gerontological Society of America. Reproduced by permission of the publisher.)

28% were in the frail group. Thus, (Fig. 2) whereas there was substantial overlap among the three related states—disability, frailty, and co-morbidity—those domains were by no means congruent, and 26.6% of those with the phenotype of frailty reported neither disability nor co-morbidity (whereas 21.5% manifested all three concurrently).

Frailty has been widely considered clinically to predict adverse outcomes. This prediction was borne out in the CHS. Among those who met the criteria for frailty at baseline, mortality was increased by sixfold for the first 3 years and more than threefold for 7-year survival (compared with those who met none of the five criteria) (Fig. 3). After 7 years, 43% of those who were frail at baseline had died, compared to 23% of those in the intermediate category and but 12% of those in the non-frail group. Additional increases associated with baseline frailty included risk of first hospitalization (96%), first fall (41%), worsening ADL disability (63%), and worsening mobility disability (71%). In each category those who were frail experienced significantly ($p < 0.0001$) greater risk of developing the condition, with those in the intermediate category at intermediate risk. Finally, those in the intermediate group at baseline had a 4.51-fold (95% confidence interval [CI] 3.39-6.00) risk of converting to the

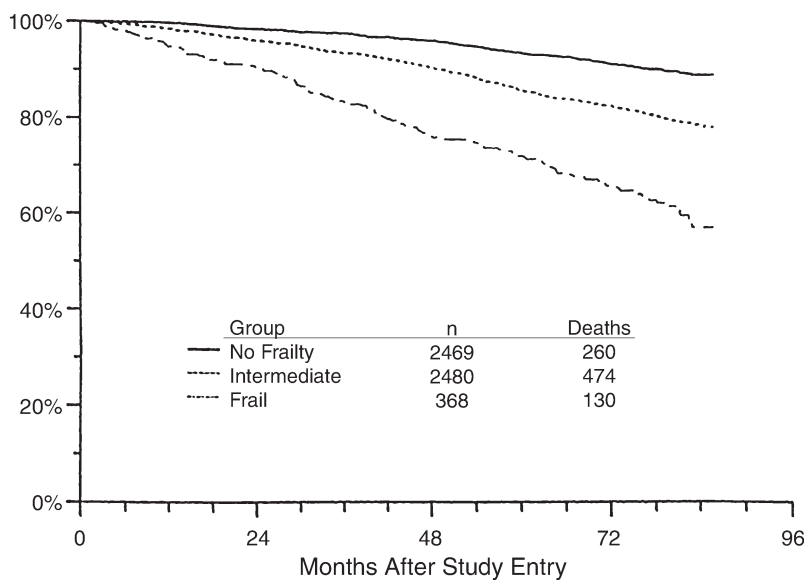


Fig. 3. Survival curve estimates (unadjusted) over 72 months of follow-up from both cohorts of the Cardiovascular Health Study by frailty status at baseline: frail (three or more criteria met); intermediate (one or two criteria met); not frail (no criteria met). (From ref. 3. Copyright © The Gerontological Society of America. Reproduced by permission of the publisher.)

frailty phenotype over the ensuing 3 years (reduced to 2.63 [1.94, 3.56] when adjusted for the co-variables of age, gender, minority status, income, smoking, brachial and tibial BP, fasting glucose, albumin, creatinine, carotid stenosis, history of CHF, cognitive function, major electrocardiogram [EKG] abnormality, use of diuretics, problems with IADLs, self-report health measures, and CES-D), relative to those in the non-frail category.

The gender-specific plight of aging women was highlighted by this study. However, whether the substantially increased risk of frailty in older women related to their lower lean body mass compared with their male counterparts or the possibility of inadequate nutrition related to living alone (or other especially prevalent female gender risks) remains a subject of speculation.

This landmark epidemiological study provides important new insights into the etiology and pathogenesis of the frailty syndrome. First, in this study frailty was strongly associated with several major chronic diseases, notably CVD, pulmonary disease, and diabetes, suggesting a possible

common pathophysiological link between frailty and these disorders. However, these associations appeared to be additive: there was a greater likelihood of frailty when two or more such diseases were present than with any single one. On the other hand, the observation that a substantial subset of those who were frail reported none of those co-morbid diseases suggests perhaps two major, alternative pathways to frailty: one reflecting physiological changes of aging not related to the pathogenesis or below the threshold for diagnosis of specific diseases (e.g., aging-related sarcopenia) and the other a final common pathway of specific co-morbid diseases as more conventionally defined.

All in all this landmark study provides strong consideration of frailty as perhaps the defining syndrome of the discipline of geriatrics. The principal limitations of this study lay perhaps in the restriction of its participants to those without limitations that would preclude their living in the community as well as those with major cognitive, affective or parkinsonian disorders, a substantial proportion of those in the patient panels of geriatricians, who might well consider them frail (4).

Nevertheless, this paper from the CHS by Fried et al. (2) especially challenges investigators to unravel the relative contributions of aging *per se* vs the development of age-associated diseases in the pathogenesis of the frailty syndrome. Moreover, it highlights the importance of developing effective strategies wherever possible to retard or reverse the downhill course leading to frailty and, at its extreme, failure to thrive. Thus, this study significantly advances definition of the clinical syndrome of frailty—including its diagnosis in a medical sense—and its associated symptoms, signs, and associated risks of adverse outcomes.

CARDIOVASCULAR DISEASE IN THE CARDIOVASCULAR HEALTH STUDY

Given the prominent role of CVD in the aggregate burden of morbidity and mortality in the elderly, it was not surprising that CVD, both clinical and subclinical, was strongly correlated with frailty as defined in the CHS. Here the report from the CHS by Newman et al. (5) offers special insight. They hypothesized that the severity of frailty among subjects in this study would be related to the higher prevalence among the frail of self-reported CVD as well a greater extent of CVD as determined by standard clinical and subclinical noninvasive testing. This prediction was borne out by their analysis of the data, especially the risk of CHF in those with frailty (odds ratio [OR] 7.51, 95% CI 4.66-12.12). Furthermore, among those without a history of clinical CVD, frailty was positively asso-

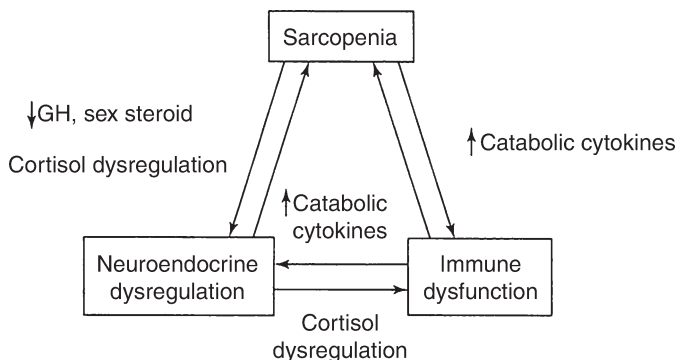


Fig. 4. Age-related physiological changes central to the syndrome of frailty. These comprise much of the basis of the poor response to stressors and vulnerability of frail persons. GH, growth hormone. (Reproduced from ref. 2 with permission of The McGraw-Hill Companies.)

ciated with several noninvasive indices of CVD: carotid stenosis greater than 75% (OR = 3.41), ankle-arm BP index less than 0.8 (OR = 3.17), major EKG abnormalities (OR = 1.58), increased left ventricular mass by echocardiography (1.16), and a higher prevalence of infarct-like lesions in the brain (OR = 1.71). Univariate analysis established significant associations between frailty and MI, angina, and claudication as well as with any CVD; on the other hand associations with transient ischemic attack, bypass surgery, and angioplasty did not reach criteria for statistical significance. Thus, whereas overt CVD was clearly associated with a higher prevalence of frailty, so was evidence of subclinical CVD in this aging cohort. This reinforces not only the centrality of CVD in its association with frailty but also perhaps shared pathophysiology in the genesis of CVD and frailty in this aging cohort.

PATHOGENESIS OF FRAILTY

Despite the prominence of CVD as well as the many other acute and chronic diseases that are so prevalent among the elderly in those defined as frail in this construct, by themselves these diseases constitute only a portion of the complex scheme depicted by Fried and Walston (2) as a summary of the pathogenesis of frailty (Fig. 1). In this scheme, these authors focus on three principal elements of age-related physiological changes that are central to the pathogenesis of frailty: sarcopenia (low muscle mass), neuroendocrine dysregulation, and immune dysfunction (Fig. 4).

Lean body mass—bone, muscle, other connective tissue, and major non-adipose organs—declines incrementally with advancing age, beginning on average at approximately age 35 and progressing with the passage of time to the point where, especially in those with frailty, up to 50% of lean body mass is lost (principally skeletal muscle), replaced wholly or in part by fibrotic and/or adipose tissue. Prior to old age, this decline is typically largely masked by the progressive accretion of adipose tissue as total body weight increases throughout middle age and into early old age, adiposity thought in large part to mediate the increased incidence of dyslipidemia, hypertension, and ultimately diabetes with advancing age, all consequences of the increased resistance to insulin conferred by obesity and in turn central to the pathogenesis of the metabolic syndrome and its CVD consequences that are so common in the older population. Generally in late middle age, the loss of lean body mass becomes balanced by the accretion of adipose tissue and total body mass stabilizes (typically beyond age 50 in men and age 60 in women). Ultimately, especially in old age (>75 or 80) net weight loss occurs with the incipient development, advent, and progression of frailty and the loss of both lean and fat mass as a cardinal feature of the syndrome. This catabolic spiral may be mediated by the loss of anabolic hormones, notably growth hormone (GH) and insulin-like growth factor (IGF)-1, as well as estrogen and androgen, that accompany both the aging process and the diseases of old age that perpetuate and accelerate this decline.

Ultimately, the major loss of muscle mass, defined as sarcopenia, profoundly limits functional capacity, especially in those in the oldest age group. This leads to decreased exercise (and energy expenditure), weakness and fatigue, and diminished ability to perform many ADLs, all features or strong correlates of the frailty syndrome. Other vulnerabilities also proceed from declining muscle mass; notably poor balance, slow gait, and increased risk of falls. Accompanying this decline in lean body mass is a progressive decrease in VO_2 max, which reflects both the decline in physical activity that is normative with advancing age in our society and, at a more basic level, the loss of lean body mass and its higher per kilogram basal energy metabolism that accompanies the aging process. This decreased energy expenditure is met with decreasing appetite (aggravated by the anorexia of aging and especially inflammation when present), which renders the elderly person vulnerable to both macro- and micro-nutrient deficiency, progressive weight loss and sarcopenia in a vicious spiral of decline. All of these changes contribute to the sharp decrease in exercise tolerance among older persons, particularly those who are pre-frail or frankly frail. The loss of lean body mass also contributes to the

decreased tolerance to fluctuations in environmental temperatures of both heat and cold experienced by older, thinner individuals.

A second limb of this frailty scheme relates to the immune dysfunction that accompanies the aging process. This includes increased vulnerability to infections as reflected in the aging organism's diminished ability to generate T-cell proliferation in response to antigenic stimulation and the reduced ability of such T-cells to secrete interleukin (IL)-2, essential to developing appropriate hypersensitivity responses, generating cytotoxic cells, stimulating B-cell proliferation and, in turn, mounting adequate humoral immunity. As noted, this immune deficiency is also aggravated by nutritional deficiency in which inflammation often plays a central role.

Thus, an essential contribution of immune dysregulation in the genesis of frailty is suggested. This dysregulation extends to impaired maintenance of the optimal balance between pro- and anti-inflammatory forces. This has in turn generated a leading hypothesis of the pathogenesis of frailty that strongly connects CVD with frailty. This reflects the prominence of inflammation in many of the major CVDs that are so common in the elderly as well as in a general tilt of the balance toward pro-inflammation with aging, generating an increased basal degree of immune activation detectable in those destined to become frail long before they qualify for the diagnosis of frailty.

The third arm of the major triad operative in the pathophysiology of frailty emphasized by Fried and Walston focuses on the neuroendocrine dysregulation associated with aging. This includes progressive dysfunction at multiple key points of neuroendocrine regulation, including a decline with aging in the extent of the very complexity that characterizes optimal physiological control. This notably includes changes in the cardiovascular system, in which the normal and perhaps optimal variation in such parameters as the cardiac cycle declines with advancing age, for example, with loss of "sinus arrhythmia, part of the pattern of "homeostenosis" or reduced homeostatic response to environmental or internal perturbations that characterizes aging. This in turn leads to increased vulnerability of aging persons to functional impairment, a reflection of their diminished ability to respond to normal stimuli and a sluggish negative feedback system.

Related to this diminished physiological complexity is increased vulnerability to stressors of a neuroendocrine nature. These include responses to physical danger, psychological distress, and pain. Diminished sensitivity to β -adrenergic receptor stimulation is a point of commonality in mediating dysfunction of this system. Moreover, the relationship between the adrenergic, cholinergic, and glucocorticoid-mediated systems appears

to be altered in advanced stages of the aging process. Baseline activities of these stress-response systems appear to be elevated with advancing age, with higher baseline sympathetic nervous system activity and tone and elevated basal cortisol levels. However, tonic basal activation appears to give way to maladaptive regulation in response to stressors, both chronic and acute. In turn, chronic overproduction of cortisol may suppress immune function, as well as produce the increased insulin resistance, increased adiposity, and loss of lean body mass that parallel advancing age. Increased baseline levels of norepinephrine and epinephrine with advancing age suggest decreased tissue sensitivity to these hormones as well as a diminished secretory response to acute stimuli. In addition, in the locus ceruleus brain center, which is primarily responsible for regulation of sympathetic nervous system activity, increased concentration of corticotropin-releasing factor may in turn contribute to increasing cortisol secretion, yet another example of the vicious cycle of interactions that may accelerate the processes leading to frailty and, when irreversible, failure to thrive.

Other hormones also affected by the aging process may contribute to frailty. GH and IGF-1 are often diminished with aging, and both are clearly reduced with the chronic diseases and diminishing vitality of the frailty syndrome. Both hormones are critical to the maintenance of lean body mass, IGF-1 being secreted in response to GH and serving as an anabolic “second messenger” in regulating lean body mass. These hormones are normally secreted in pulsatile fashion; however, consistent with the general loss of complexity in biological systems with advancing age, this pulsatile secretion is progressively dampened during the aging process. In turn, through diminished IGF-1 levels, this decrease serves to reduce lean body mass of both muscle and bone. Encouragingly, supplementation of GH in older men with lower IGF-1 levels appears to produce a (small) increase in lean body mass. However, this has not been demonstrated to result in increased strength or endurance during 6-month trials, and hence GH therapy is by no means a panacea for the weakness of old age or the frailty syndrome.

Sex hormone secretion is also diminished with advancing age. This occurs most dramatically with ovarian failure across menopause in women, a sharp decrease followed by both a rapid decline in bone mineral density and also a more subtle yet clear decrease in other components of lean body mass and their replacement by adipose tissue. Males also experience diminished sex steroid secretion with aging. Although this decline is much more subtle than that in perimenopausal women, the gradual decrease in testosterone levels and increasing hypothalamic sensitivity to the nega-

tive feedback of testosterone conspire to diminish the anabolic effects of male hormone (especially free testosterone, which declines more than the total, attributable in large measure to increased secretion of sex hormone-binding globulin with advancing age). This contributes to the decrease in both bone and, especially, muscle mass in aging men.

Declining regulation of adrenocortical secretions also contributes to reduced endocrine efficiency with advancing age. Perhaps the most dramatic change in this regard is the decline in secretion of dehydroepiandrosterone. Levels of this steroid hormone peak at adolescence and decrease progressively thereafter across the remainder of the life span. The clinical significance of this decline remains controversial, however, although it has been suggested to contribute to the diminished suppression of the catabolic or inflammatory cytokines (notably IL-6, IL-1 β) and increased induction of immune stimulatory cytokines such as IL-2 that accompany aging.

Other metabolic pathways whose efficiency declines with advancing age and contribute to the decrease in fine neuroendocrine regulation with advancing age include those serving other critical homeostatic functions, including regulation of body weight, appetite, thirst, and temperature.

The interaction of the three elements of this triad—lean body mass (and sarcopenia and osteopenia), immune dysfunction, and neuroendocrine dysregulation—is also critical in the complex pathogenesis of frailty. Thus, a vortex of mutually reinforcing dysregulation of these critical homeostatic systems may develop in an ever-accelerating cycle, ultimately placing the individual at grave risk for an irreversible terminal cascade. Whereas in many instances this may progress in a gradual and seemingly seamless fashion, a more dramatic cascade is perhaps more familiar to the geriatric clinician, a tragic decline initiated by a “trigger event.” For convenience, such inciting stimuli have been grouped under the mnemonic of infections, infarctions, and infractions (the last including falls and fractures, other trauma including surgery, metabolic or other consequences of homeostatic collapse, and pharmacological and other iatrogenic misadventures). Alternatively, this pathogenetic scheme may be ultimately classified as attributable to “primary causes” or “secondary causes.” Primary causes, currently under increasing basic investigation, focus on fundamental, time-related changes in response to the patterns of DNA that define each individual, oxidative or other changes to that DNA, and the shortening of telomeres that accompanies cellular replication to a critical point beyond which renewal through subdivision is no longer possible. Alternatively, secondary causes of frailty, more apparent clinically, include the association of frailty with the myriad of problems and diseases that are common in old age, notably including CVD and its throm-

boembolic or arrhythmic complications but also extending to malignancy, chronic infections, and even depression as well as vulnerability to the trigger events that are so common in the elderly and especially among those who are frail.

INFLAMMATION: NEXUS OF THE PATHOGENESIS OF FRAILTY

As introduced previously, an altered balance between pro- and anti-inflammatory cytokine genes and levels of cytokine production during the aging process may result in a state of chronic, often subclinical inflammation in the elderly, especially those on the brink of frailty. This has been suggested explicitly in reports such as those by Hamerman (6), Cohen (7), and Ershler (8). This central hypothesis includes the possibility that this level of smoldering inflammation results from activation of the immune system through chronic, indolent infectious processes, such as periodontal disease, chronic pulmonary disease, diverticulitis or cholecystitis, chronic renal disease, and urinary tract infection, all conditions associated with inflammation that are chronic in nature and increase in prevalence with advancing in age. Alternatively, against this perhaps more traditional, infection-driven pathogenesis of enhanced inflammation with age is the suggestion that part and parcel of the aging process is loss in fine regulation of the immune system such that the carefully modulated balance between pro- and anti-inflammatory processes maintained throughout healthy, effectively symptom-free adulthood tips toward the “pro side,” resulting in subclinical chronic inflammation even in the process of “normal” aging. The markers of inflammation most studied in this respect have been the cytokine IL-6 and other cytokines even earlier in the cascade such as IL-1 and tumor necrosis factor- α . Perhaps yet more studied have been the acute phase reaction proteins, serum amyloid A (SAA), fibrinogen and, especially, CRP (Fig. 5). Indeed a number of studies have directly tied changes with aging in primary indices of physiological efficiency and vulnerability and even functional status with aging to changes in these proteins, which are essential to optimal immune regulation. Moreover, increased levels of CRP and other acute inflammatory markers are commonly seen in the other chronic diseases associated with the frailty syndrome outside of the domain of CVD, notably chronic disease of the systems noted above in the CHS, including such pervasive conditions in frail patients as depression (e.g., in the CHS, depression was associated with an increased CRP level [9]).

Perhaps of greatest fascination to cardiologists, however, are observations relating inflammation to the pathogenesis of the CVDs that are so

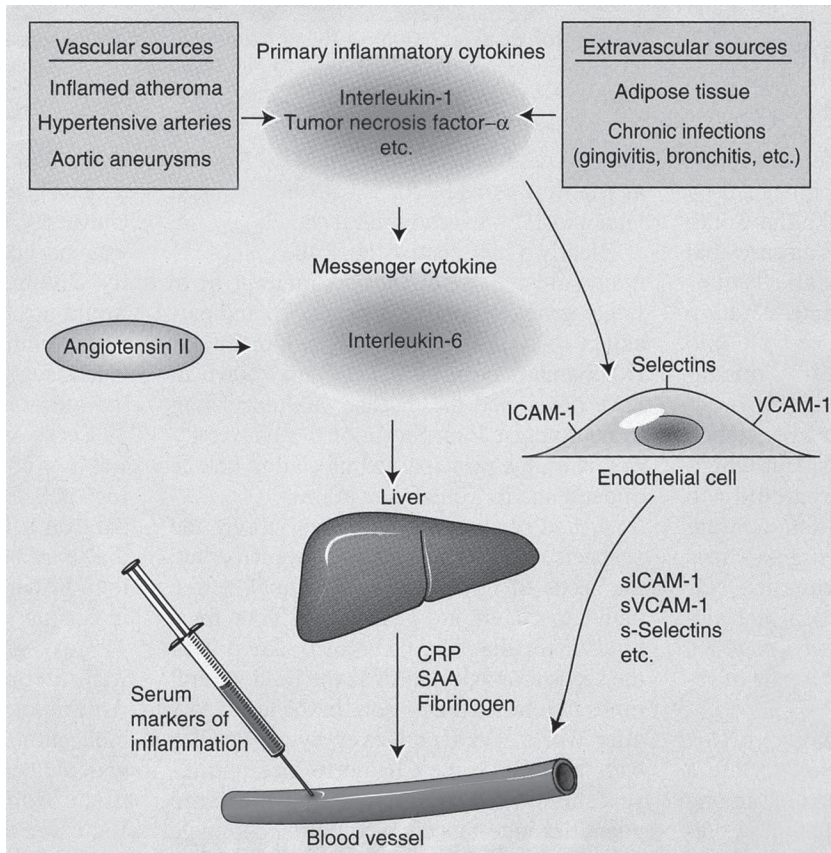


Fig. 5. Pictorial summary of the major elements of the inflammatory cascade that is hypothesized to contribute to atherothrombotic cardiovascular disease and, more generally, the pathogenesis of frailty. ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; CRP, C-reactive protein; SAA, serum amyloid A. (Reproduced with permission from ref. 8a.)

common in the elderly and especially prevalent among the frail. Ridker (10) has especially championed the central role of CRP as a marker as well as, far more controversial (11), perhaps even a mediator of CVD at all ages and especially among the elderly, given the exponential rise in CVD with advancing age.

CRP: A KEY LINK BETWEEN CVD AND FRAILITY

The acute-phase response encompasses a broad array of biochemical changes mounted by endothermic organisms following various causes

of tissue damage, including trauma, infections, and malignancy, all processes that generate an inflammatory response (12). Cytokines present at the site of the damage upregulate the (mostly hepatic) synthesis of multiple proteins, including complement, coagulation factors, proteinase inhibitors, and transport proteins (and downregulate others, notably the apolipoproteins of LDL and HDL). The first of those proteins to be described (in 1929) and that which responds most dramatically, however, is the CRP (SAA is close to CRP in this regard).

CRP in plasma originates exclusively from the liver (although tissue CRP may arise locally), where it is under the transcriptional control principally of IL-6. The median concentration of CRP measured by the highly sensitive (hsCRP) assay in healthy young blood donors is 0.8 mg/L, with a 90th percentile at 3 mg/L and 99th percentile at 10 mg/dL. A handy rule of thumb has evolved: below 1 mg/dL is normal, between 1 and 2 borderline, and above 3 is increased. CRP levels appear remarkably constant in a given individual in a stable state of good health (comparable to the stability of cholesterol concentrations and similarly under strong but complex genetic control). Coupled with its stability during storage, this has made CRP the focus of multiple “instant” prospective studies when measured in stored samples from longitudinal epidemiological and clinical studies. This stability is all the more extraordinary given the rapidity and degree of CRP elevations following a single acute stimulus: serum levels exceed 5 mg/L within 6 hours and peak at concentrations as high as 10,000 mg/L at 48 hours. With an unvarying half-life of about 19 hours, the CRP synthesis rate alone effectively determines the plasma concentration. However, not all stimuli to CRP are acute and transient; perhaps more common and subtle are subacute or chronic inflammatory stimuli (especially relevant to gerontology and geriatrics). Therefore, investigators pursuing CRP as an index of tissue damage and inflammation following an acute insult (e.g., MI) advise waiting at least 6 weeks after such an event to judge whether CRP levels have returned to baseline and the acute inflammatory stimulus has completely abated.

The relationship between CVD and inflammation has enjoyed a crescendo of investigative and clinical interest in recent years. Historically, atherogenesis was conceptualized as a chronic, insidiously progressive process. However, the failure of standard indices of CVD risk—classically smoking, BP and cholesterol (even when fractionated into HDL, LDL, and very low-density lipoprotein)—to account for more than 50% of the risk of heart disease in a given individual has long suggested that additional pathogenic factors were at work. Atherosclerosis began to be appreciated as a more dynamic process, one under more complex regulation, in the latter third of the 20th century in the research of Ross (13) and

others. These researchers investigated the pathogenesis of atherosclerosis according to the “reaction-to-injury” hypothesis originally proposed over a century earlier. The stimulus to examine CVD as a more dynamic process in such studies received major clinical impetus from demonstration of the rapid development of new lesions on coronary angiography repeated at relatively close intervals in patients with recurrent and progressive CVD. At a more basic level, the dynamic nature of the disease was confirmed in studies of atherosclerosis in experimental models. Those especially focused on the role of the arterial endothelium in modulating both chronic atherogenesis and also the acute response to arterial ischemia and occlusive thrombosis—itsself an intense stimulus to inflammation. Indeed, atherosclerosis has come to be considered an intrinsically inflammatory disease process (13).

This hypothesis received major support in the past decade in a burst of observational epidemiological studies, both cross-sectional and longitudinal, and even in clinical trials of anti-inflammatory agents in CVD prevention, progress dramatically propelled by development of the hsCRP assay. These studies included the landmark Physicians Health Study, which disclosed an increased (2.9-fold) risk of MI and (1.9-fold) of stroke in healthy middle-aged male doctors in the highest vs. the lowest quartile of CRP levels (14). A similar relationship was reported in participants in the Women’s Health Study (15), in which baseline CRP levels were linearly correlated with incident CVD (2.3-fold higher in the top vs bottom quartile). Especially germane to this chapter on frailty, a nested case–control study within the CHS also suggested that baseline CRP levels predicted incident CVD, including angina, MI and death (16). Here, however, the association of higher CRP levels with CVD events was especially pronounced for risk of MI in those with subclinical disease (OR 2.67 [CI = 1.04–6.81]) and notably more in women (4.50 [CI = 0.97–20.8]) than men (1.75 [CI = 0.51–5.98]), and case–control differences were greatest when the interval between baseline and the CVD event was shortest (implying a more active inflammatory state at baseline).

Indeed atherogenesis has emerged as a complex, smoldering, stuttering, dynamic process in which inflammation is both a cause and a result of tissue damage. Atherogenesis may be accelerated by the release of pro-inflammatory stimuli such as IL-6, IL-1- α , and TNF α from extravascular sites such as adipose tissue (contributing to insulin resistance) and tissue macrophages (17,18) as well as from vascular sites in the arterial wall and the heart itself. These in turn trigger the hepatic synthesis and release of acute phase proteins (notably CRP, fibrinogen, and SAA) that not only signal but may also participate in the pathogenic spiral. As reported by

Lindahl et al. (19), the magnitude of tissue necrosis from atherothrombotic events such as frank acute MI or even more subtle damage in patients with unstable coronary artery disease as reflected in serum troponin levels during the first 24 hours after presentation continue to predict future cardiac death for months and years. However, just as predictive are the parallel rises in CRP and fibrinogen in such patients. In a nested case-control study, these markers of inflammation also predicted future coronary events in hypercholesterolemic men in the West of Scotland Coronary (primary) Prevention Study (20). A third marker, lipoprotein-associated phospholipase A₂ (platelet-activating factor acetylhydrolase) was also independently related to future risk in the same study. This enzyme, which circulates bound to both LDL and HDL, is regulated by mediators of inflammation and has been suggested to generate inflammation-promoting lysolecithin from LDL, thus inducing a direct inflammatory effect of circulating LDL (21). Other factors generated by inflammatory stimuli, such as infectious diseases resulting in release of lipopolysaccharide that oxidizes LDL and increases pathogenic oxygen radicals in the vessel wall, have also been implicated in a process that not only promotes atherogenesis but also destabilizes the atherosclerotic plaque, leading to its rupture and occlusive thrombosis of the overlying lumen (21,22).

Thus, a vicious cycle can be set in motion by forces that produce tissue damage, inflammation, atherogenic changes in lipoproteins and the arterial vessel wall, subclinical atherosclerosis, and atherothrombotic complications, which produce tissue damage, and so on. The major feature of this pathophysiological scheme appear now to have reached scientific consensus (24), with contemporary controversy centering on whether the markers of inflammation, notably CRP, serve as mediators as well as markers of the process (25).

INHIBITORS OF INFLAMMATION IN CVD PREVENTION: THE PROMISE OF HMG-CoA REDUCTASE INHIBITORS

The therapeutic implications of a central role for inflammation in atherogenesis and atherothrombotic disease have also drawn intense interest. It has been suggested that statins, hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, may have a dual role in CVD prevention, both by lowering LDL cholesterol through inhibition of cholesterol synthesis and also by reducing inflammation. This may directly retard the atherogenic process if indeed CRP is a mediator as well as a marker of the disease (25). In support of its direct role, for

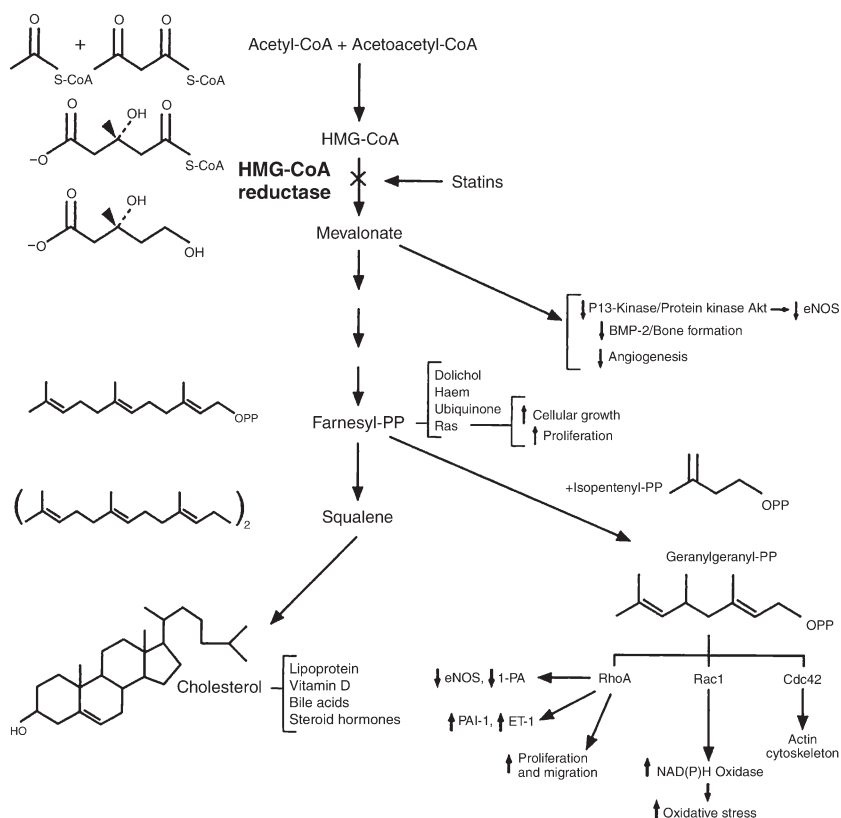


Fig. 6. Biochemical scheme of the generation of cholesterol and isoprenoids from acetyl-coenzyme A (CoA) and acetoacetyl-CoA in this complex process by inhibition of HMG-CoA reductase by statins, consequent decreases in cholesterol derivatives and signaling molecules such as Ras, Rho, and Rac, and changes in turn in the systems they modulate. (Reproduced with permission from ref. 26.)

example, CRP has been reported to bind to modified LDL in atherosclerotic plaques, in turn activating complement, which contributes to atherosclerotic lesion progression. CRP has also been reported to impair endothelial function by decreasing endothelial nitric oxide synthase (eNOS) in cultured cells, a process mediated by Rho. Here the pleiotropic potential of the HMG-CoA reductases offers special promise (26–28) (Fig. 6). Inhibition of HMG-CoA reductase decreases the synthesis not only of cholesterol but also the isoprenoid geranylgeranyl-pyrophosphate, which

facilitates membrane lipid attachment of Rho and the membrane translocation of Rho/Rho kinase. Thus, both directly and also possibly indirectly (by decreasing inflammation and CRP synthesis) statins appear to increase eNOS expression and activity, modulating endothelial cell function in an anti-atherogenic direction. Reduction in Rho by statins also appears to enhance endothelial function by decreasing endothelin-1 and expression of the AT₁ receptor as well as decreasing thrombosis by increasing expression of tissue-type plasminogen activator and diminishing plasminogen activator inhibitor 1 (27).

Statins have also been suggested to exert primary reduction of inflammation by inhibiting production of the pro-inflammatory cytokines IL-6, IL-8, as well as the monocyte chemoattractant protein measured in peripheral blood mononuclear cells and human umbilical vein endothelial cells (29).

Additional potential for a bimodal role for statins in CVD prevention has been suggested from a growing number of studies demonstrating that hsCRP and LDL cholesterol levels contribute independently and sometimes synergistically to CVD risk (24). For example, in the AFCAPS/TexCAPS primary prevention trial, lovastatin reduced CRP levels by 15% in women, a decrease not related to their induced changes in the lipid profile. In this study, lovastatin decreased events not only in subjects at increased CVD risk by virtue of a total cholesterol/HDL cholesterol above the median (regardless of CRP level) but also in those with above median CRP (but below median total/HDL cholesterol ratios), while not reducing CVD among those with below median values for both. This led the authors to suggest that measurement of CRP in addition to lipids might permit targeting statin therapy to those most likely to benefit on either or both axes of risk (30).

However, as attractive as the simplicity, relative safety, and pleiotropic efficacy of statins in CVD prevention appears, it is important to emphasize other ways to reduce CRP that are not confined to anti-inflammatory pharmacological interventions above. Indeed simply withdrawing drugs that raise CRP levels may reduce risk: oral contraceptives and postmenopausal estrogen/progestin hormone replacement therapy (HRT) raise CRP levels (31), and HRT has been specifically associated with increased CVD risk in both secondary (Heart and Estrogen/progestin Replacement Study [32]) and primary (Women's Health Initiative [WHI; 33]) prevention trials. Hence, the plummeting use of HRT following release of the unexpected adverse results of the WHI may serve to reduce CVD risk in postmenopausal women. Interestingly, transdermal estrogen replacement therapy does not appear to increase CRP, suggesting a specific role of

first-pass hepatic exposure to the estrogen–progestin combination in raising CRP levels (34) (and potentially CVD risk). Lifestyle interventions also appear to hold promise for CVD prevention via lowered inflammatory burden and reduced CRP levels: the combined effect of dietary changes and increased exercise reduces both weight and indices of inflammation, including CRP, offering promise of reduced CVD (35).

Thus interventions to reduce inflammation within the cardiovascular system offer special promise of reducing atherothrombotic disease in the elderly. However, such interventions may hold additional opportunities to reduce CVD in the elderly beyond the atherothrombotic realm. This appears especially to be the case for CHF, the most common cause for hospitalization among Medicare beneficiaries and the bane of the professional lives of so many cardiologists, geriatricians, and geriatric cardiologists. Here once again the CHS lends special insight (36). Over the average of 5.5 years of follow-up in subjects 65 to 100 (mean age 73 ± 5) the incidence of CHF was 19.3/1000 person-years, a rate that increased progressively with age and was greater in men than women. Beyond age and sex, the leading factors in the population—attributable risk of CHF in this study included a high level of CRP (9.7%) as well as prevalent CHD (13.1%) and systolic hypertension (>140).

This finding received support in a study of the incidence of CHF in more than 732 Framingham Study subjects (mean age 78, 67% women) free of prior CHF or MI (37). CHF developed in 56 subjects after a mean of 5.2 years. Three indices of inflammatory activation were measured: serum IL-6 and CRP levels and TNF- α production by peripheral blood monocytes. On multivariable analysis higher levels of each of the three predicted increased risk of CHF. CRP of at least 5 mg/dL was associated with a 2.8-fold elevation, which when combined with IL-6 and TNF- α above the respective medians was raised to 4.07 (95% CI 1.34–12.37).

Hence increased baseline indices of inflammation over and above those attributable to either clinical or subclinical atherosclerosis appear to increase risk of CHF, suggesting that this often lethal complication may reflect a more general inflection toward a pro-inflammatory status.

CVD, DISABILITY, AND FRAILTY: CLOSING THE CAUSATIVE TRIANGLE IN THE ELDERLY

Thus a prominent role of inflammation in mediating the CVD that escalates exponentially with time and aging appears increasingly clear. However, it also seems likely that inflammation plays a broader and more central role in mediating the progressive vulnerability and dimin-

ished resiliency that accompanies the aging process and leads to frailty and ultimately failure to thrive.

One index of this inflammatory burden is the gradual rise in population CRP levels (and other indices of inflammatory activation such as IL-6) seen with advancing age. Whereas this has often been attributed simply to the gradual accumulation of age-related diseases and their inflammatory pathogenesis, it appears that generally aggregate increased pro-inflammatory activation from both disease and aging per se may mediate the decline more directly at multiple points in the complex cascade of frailty illustrated in Fig. 1 and the Venn diagram that quantifies the triad of frailty, co-morbidity, and disability in the CHS depicted in Fig. 2. A growing number of epidemiological studies support this hypothesis. For example, the report by Ferrucci et al. (38) from the Iowa site of the Epidemiologic Studies of the Elderly (EPESE) (subjects > 71 years) suggested that participants who were in the highest (vs lowest) tertile of IL-6 levels were 1.76 times (95% CI, 1.17–2.64) more likely to develop mobility-disability and 1.62 times (1.02–2.60) more likely to develop mobility-plus-ADL disability, with a progressive rise in risk with increasing IL-6 concentrations. A decline in physical performance in subjects with higher levels of CRP and IL-6 was also seen in the MacArthur studies of Successful Aging, a subset of the EPESE populations (39) that included 880 high-functioning men and women. Higher levels of CRP and IL-6 were seen in less active persons, and on multivariable analysis, low levels were seen in participants with higher walking speed and greater grip strength. Similar findings were reported at a more mechanistic level by Barbieri et al. (40), who suggested that high circulating IL-6 levels and low IGF-1 are synergistic for poor muscle strength (IL-6 directly impairing muscle IGF-1 gene and protein expression), leading in functional terms to disability and increased mortality risk in older women (41). Roubenoff et al. (42) came to similar conclusions from analysis of cytokines and IGF-1 and their relationship to sarcopenia and mortality in very old Framingham Study participants.

Returning to the Iowa EPESE population, the association of higher IL-6 levels with increased disability in this population also extended to an increased risk of mortality (43): IL-6 in the top quartile was associated with a twofold greater risk of death compared with the lowest quartile; higher CRP levels also predicted 1.6-fold higher mortality, while elevations of both increased risk of death 2.6 times, with equivalent increases for death from cardiovascular and non-cardiovascular causes. Similar findings were reported from the Duke population within that group of studies (44): the 5-year relative risk for death with IL-6 in the top quartile

was 1.28 (0.98–1.69). Moreover, perhaps of special interest to cardiologists, increased coagulation diathesis as one of the cluster of factors triggered by inflammation also appeared to contribute to risk of functional decline and mortality in this population. D-dimer levels predicted a 1.53 fold higher risk of death, whereas individuals in the top quartile of both IL-6 and D-dimers had a twofold risk. Of note, the 4-year follow-up of the functional status of subjects in this population also disclosed a doubling of risk of decline in Katz ADLs and IADLs for those in the top quartiles of both indices.

A similar pattern was observed in the longitudinal data from the MacArthur Research Network on Successful Aging Community Study derivative of the EPESE study (45). This added two additional markers of inflammation to the list of such indices of frailty often noted by clinicians beside upper tertiles of IL-6 (>3.8 pg/dL) and CRP (>2.65 mg/L): a low serum albumin (<3.8 g/dL) and a low serum cholesterol (<170 mg/dL, bottom decile). In subjects with three or four (vs none) of these markers of inflammation adjusted odds ratios for 3- and 7-year mortality were 3.2 and 6.6, respectively.

Finally, to close the triangle with specific reference to the CHS in which the frailty syndrome was defined, frail (vs non-frail) subjects had increased mean levels of CRP (5.5 ± 9.8 vs 2.7 ± 4 mg/L) as well as higher levels of coagulation factors VIII and D-dimer (46), differences that remained after exclusion of diabetes and subjects with CVD and adjustment for age, sex, and race. Thus inflammation and markers of coagulation are increased in frailty even in the absence of prevalent CVD.

INFLAMMATION IN THE TRANSITION FROM FRAILITY TO FAILURE TO THRIVE

Thus, inflammation appears to play a central role in the downward spiral from robust health to frailty to failure to thrive through its contributions to sarcopenia, neuroendocrine dysregulation, and immune dysfunction as well as CVD and the other co-morbidities and disabilities that are so prevalent among the failing elderly. For cardiologists, this is perhaps most apparent in the atherothrombotic disease so common among their clientele. But especially for those (especially geriatric) cardiologists whose patients have typically survived previous MIs, angioplasties, and coronary bypasses and now manifest heart failure and the pernicious multisystem effects of chronic inflammation and the weight loss, weakness, exhaustion, slowness, and low activity that constitute the classical pentad of frailty, understanding the pathophysiology of this syndrome is central to their practice. Such understanding also underscores the need

to investigate frailty with special focus on potential intervention strategies. Here the evaluation of anti-inflammatory agents (47), including statins, represents an attractive approach.

Finally, cardiologists, especially geriatric cardiologists, must learn to recognize when the downward spiral has gone beyond the point of no return and failure to thrive supervenes—and a transition to a palliative approach to care of the patient is most appropriate and humane.

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