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REVIEW ARTICLE

A Conceptual Framework of Frailty: A Review

Walter M. Bortz II

Stanford University School of Medicine, California.

This article presents an overview of the increasingly common condition of frailty, which by and large lacks clarity of definition. A variety of sources provide this statement regarding definition, incidence, causation, rate, and time of appearance. Utilizing the newly elaborated process of symmorphosis, which explains the coadaptation of structure and function secondary to altered energy loads, I propose that frailty is a body-wide set of linked deteriorations including, but not confined to, musculoskeletal, cardiovascular, metabolic, and immunologic systems. The common final pathway that leads to this constellation of findings is usually keyed to a decline in physical activity either as a result of habit or disease inputs. As such, the state of frailty is largely separable from the process of aging and should thereby be susceptible to active intervention and reversal.

THE emergence of frailty as an increasingly common physical state prompts inquiry into what it is. Is it a disease? Many persons are frail, yet lack a specific diagnosis. Is it aging? Some young people are frail, and some old people aren't. Is it inevitable? Its occasional reversibility negates this suggestion. Is it functional or structural? Is it single- or multi-system in its nature?

A recent review article states "frailty does not have a precise scientific meaning" (1). Gillick observed "frailty is a syndrome in desperate need of description and analysis" (2). Elsewhere, Fried and colleagues observed that a standardized definition has not been established (3). "In fact, identification of the criteria for frailty has been found to be a highly complex and demanding task" (4). This article introduces a recently elaborated process, symmorphosis, which provides an organizing framework for understanding frailty into which numerous seemingly separate aspects can be incorporated (5). Further, insights provided by this formulation lead directly to the understanding of pathogenetic mechanisms and thereby preventive and therapeutic approaches.

Defining Frailty

Various operational schemes have been employed in seeking a definition for frailty. Some proposals mention the participation of diverse disease states in the production of frailty (6–8). Others suggest biochemical modulators as central to the frail state (1,9,10). Several efforts approach frailty in thermophysical terms (11,12).

The interplay of frailty, dependence, and disability has been commonly noted (13). Intrinsic to these attempts to define frailty is the recognition that frailty connotes diminished reserve capacity and thereby increased risk (14,15). The degree of reserve loss and increase in risk show both presymptomatic and symptomatic phases as described below. Such recognition has huge financial and public policy implications, lending further urgency to the development of a simple, robust, and practical definition of frailty.

Medical science seeks parsimonious explanations. Such reductionistic methodology has borne much fruit, but also has its limits. While most pathology is described in terms of component failure, other explanatory efforts use the "system" as their reference point. Cannon, Selye, and others regard the organism as a whole, a set of unified systems that in turn are buffeted by a wide array of perturbing forces including the generic processes of stress and disuse (16–19). The systematic effects of these two disruptions have been codified within the rubrics of the General Adaptation Syndrome and the Disuse Syndrome, respectively (17,20). Each of these has well-defined and empirically validated components. A recent editorial titled "In Search of the Underlying Mechanisms of Frailty" projected that a full understanding may result from a description of how multiple systems intersect to produce frailty (21). Fried and Walston have proposed a "cycle of frailty" in which musculoskeletal, neuroendocrine, nutritional, and immunologic defects are combined in a "systems" approach to the definition (22).

Such a "cycle" or "cascade" of frailty acknowledges the participation of a wide range of secondary chemoregulations, growth factors (10,23), hormones (9,24,25), and cytokines (21,26) in the production of the frail state.

The recent introduction of the term symmorphosis by Wiebel and colleagues serves as a powerful explanatory mechanism for frailty (5). Symmorphosis describes how different body structures and functions coadjust to different levels of organismic energy flow (27). Both the multicompartment oxygen and digestive and metabolic fuel delivery systems exhibit tightly linked structural and functional changes of their component parts in response to organismic input. For example, physical exercise increases oxygen requirements of the body many-fold over baseline needs. In response cardiac output, capillary density, blood hematocrit, and muscle mitochondrial number and enzymatic capacity each are quantitatively linked to the energetic stimulus. This is usually measured as the global parameter known as $\dot{V}O_2$ max. Similarly, enzymes involved in the digestive and metabolic pathways covary in response to substrate supply, leading to the notion of a metabolic network in which control is generally distributed instead of the previously held rate-limiting, single-step concepts. The energy transduction and gene expression details of these processes are becoming progressively defined (12).

The reconceptualization of multiple system interrelationships as an appropriate explanatory scheme for life process unifies structure and function and thereby provides a sturdy framework for the definition of frailty. As symmorphosis defines the anabolic process of building structural capacity to meet demand, it follows that lessened load, as with physical inactivity, leads to linked and parallel losses in form and function. Decreased physical activity leads to muscle weakness and bone fragility; decreased oxygen throughput, decreased arterial size, increased clottability, and altered blood lipid levels; metabolic inefficiency, decreased glut transporters, obesity, Type II diabetes; and immunologic decay.

Older persons move less. This may be the result of habit or because of limitation imposed by disease conditions. But whatever the etiologic agency, the lessened physical activity seen with most older persons initiates body-wide sets of negative outcomes that further conspire to accelerate the deteriorative processes. Frailty is herein defined as a state of muscular weakness and other secondary widely distributed losses in function and structure that are usually initiated by decreased levels of physical activity. Such depiction describes many of the feedback features that are inherent in frailty, yet muscle weakness remains the central obligate feature of the term.

Incidence

The multiplicity of approaches in defining frailty precludes reliable estimation of its incidence. One recent calculation places the number of frail persons in the United States at 6 million (28). But whatever definition is employed, this number represents an underestimate. Twenty-seven percent of 985 patients who were admitted to the Palo Alto Veterans Hospital and were older than 65 were judged to be frail (29). Importantly, too, the group showed a 45% 1-year mortality. A broad survey of community-dwelling persons revealed that the incidence of frailty increased from 4.8% of 65-year-olds to 56.3% for 90-year-olds (30). Fried cites data that indicate that 10% to 20% of persons older than 65 years of age are frail (4). A 1990 report of the Council of Scientific Affairs of the American Medical Association projected that 46% of community-dwelling persons older than 85 are frail (31). A recent paper from the Mayo Clinic, which used a rigid criterion for diagnostic inclusion, reported that 6% to 15% of the population of Rochester, Minnesota older than 65 years of age had diminished muscle mass (32). These values reached 40% for men older than 80 and 18% for women older than 80. The public health implications of these statistics command increasing attention, particularly because frailty is documented not to be inevitable and is reversible by active intervention strategies (33,34). The category of "active life" was resumed by one fifth of older persons who had earlier been classified as "inactive" by virtue of compromised functional status (35).

Biology of Frailty

Commonly explored in broader efforts at defining frailty is the concept of "tendency to fail," which connotes a range of capacity of the organism and all its component parts and functions before frailty occurs. The intimate participation of muscle strength in the central function of $\dot{V}O_2$ max is a salient observation (36).

All organ systems exhibit redundant structure and function. Such excess capacity serves the organism well when environmental perturbation occurs. There is a large preclinical range before symptoms occur. The World Health Oranization has described frailty as the state when "awareness" of a problem arises (37). Woodhouse lamented not only the definitional imprecision of frailty but also the lack of any quantitative estimate to it (38).

Review of a wide range of body systems consistently reveals that 30% of normal function represents a threshold for adequate function (39). Across most organ systems, there is a 70% margin of loss before evidence of failure presents. This estimate conforms generally to "safety factors" identified by Diamond in a wide range of biologic structures across animal species ranging from squid to mammals (40). This threshold value therefore identifies when reserve loss and risk increase to present symptomatic awareness (Figure 1). Oxygen transport ($\dot{V}O_2$ max) (41), myocardial oxygen consumption (42), arterial cross-sectional area (43), hemoglobin oxygen dissociation (42), maximum breathing capacity (44), forced expiratory volume (45), hematologic values (platelet, white blood cell count, prothrombin level) (42,46), hepatic and renal function (46), blood sugar, sensory capacity (vision and hearing) (47,48), cognitive skills (49), and brain dopamine content (50) each exhibit approximately a 70% functional safety margin. Other parameters such as red blood cell mass and nerve conduction velocity have lesser redundancy. Such range has been recognized elsewhere as Pendergast and colleagues state that 35% of maximal composite function equals minimal function (6). Verdery calls the range between 20% and 40% of maximal function as the disability to survival range (51). This reserve capacity is similar to that which is specified by civil engineering codes (52). Also, it is in this range of diminished function where most medical encounters and costs are generated. It seems likely, too, that the 30% of baseline barrier is the moment when active life expectancy becomes inactive life expectancy. The notion of a threshold value when frailty first presents has been previously noted (22,53).

Oxygen transport capacity as measured by $\dot{V}O_2$ max determination is a central biomarker. Muscle use, as physical exercise, is undeniably involved in this basic function, but all body systems participate in the altered physiologic loads applied by exercise as defined by symmorphosis (5). Hammond and Diamond invoke this principle in their observation of a 4- to 5-fold scaling ratio of maximum/basal energy transport capacity across different species (54).

Yet when establishing a quantitative estimation of frailty, it is the musculoskeletal system where the numerical range is most pertinent. Although all organ systems may present a range of diminished function, one does not generally refer to the individual with defective cardiac, or hepatic, or sense, etc., capacity as frail. On the other hand, a person can have otherwise intact organ functions but if musculoskeletal wastage occurs, frailty is generally acknowledged. Bassey and colleagues have shown that young persons possess 5 W/kg muscle power in the legs (55). To walk, 1.2 W/kg is required (24% of baseline), and below 0.5 W/kg (10% of baseline), movement becomes impossible. This range of diminished function conforms with many other body systems

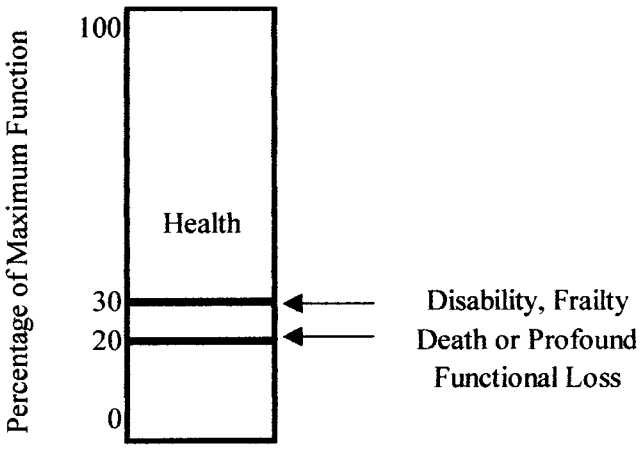

Figure 1. Frailty threshold.

and functions as noted above, but is more relevant because decreased power is central to the definition of frailty. Numerous researchers have emphasized the functional correlations of frailty with impaired activity of daily living (ADL) and instrumental activity of daily living (IADL) ratings (5,56). The ability to move is clearly central to these basic functions. Related to this is also the fact that loss of leg strength was noted to be the strongest single predictor for subsequent institutionalization, stronger than other physiologic markers and disease diagnosis (56). Similarly, Guralnik and colleagues found that lower extremity function was highly predictive of subsequent disability in nondisabled community older persons (57). This prediction held even for those in the higher functioning category. They further commented that "it is unlikely that disease status alone would predict subsequent disability." Clearly, deficits in any of the other systems can impair function of the musculoskeletal system directly or indirectly. Loss of movement capacity, in turn, frequently accelerates declines in other systems, which in turn feed back on ability to move (58). Receptor sites are down regulated, hormonal and growth factors diminish, nutritional cues are lost, circulatory competence deteriorates, sleep becomes disrupted, depression looms, and a whole cascade of catabolic events occurs. But it is the musculoskeletal system that is the entry pathway for frailty. The precise molecular details of muscle formation and breakdown are now known in great detail (59). Anything that adversely affects the anabolic and catabolic balance of skeletal muscle may provoke frailty.

Causes of Frailty

Several papers explore the causative elements of frailty (3,5,20). In essence, they jointly identify four principle etiologies: (i) genetic, (ii) disease and injuries, (iii) lifestyle, and (iv) aging.

Genetic Disorders

Whereas errors in the genetic program can contribute to frailty either through primary muscle, bone, or neurologic malformation, or secondarily through many other entities, such as sickle cell anemia or cystic fibrosis, Strohman estimates that only 2% of illness is monogenic in origin (60). It would appear that genetic misinformation is not a major singular contributor to the state of frailty (61).

Diseases and Injuries

These acute events clearly conspire in major ways to provoke frailty. Their mode of action is often abrupt and is hopefully reversible. Toxins, infections, injuries, and malignancy all may provoke frailty. Osteoarthritis, the result of repeated microinjuries, is a major form of this mechanism (62). Toth and Poehlman recently pointed out how many chronic diseases common in older people conspire to limit physical exercise and thereby accelerate catabolic processes (63).

Lifestyle

I feel that, quantitatively, the greatest contributor to frailty is lifestyle (64). Nutritional problems, either as insufficient (65) or excessive (66) calories, are frequent coconspirators in the production of frailty. The epidemic incidence of type 2 diabetes, particularly in older persons, is clearly labeled as a lifestyle pathology (67). A sedentary lifestyle leads slowly and inexorably to diminished muscle strength and frailty, so that at age 70 and beyond, the average "usually" aged person is confronted with decreased movement capacity and the above-described sequential problems. The direct burdens imposed by nutritional and exercise maladaptations are compounded by disordered chemoregulator patterns (9,10,21,23–26). Numerous population surveys reveal the endemic inadequacy of physical activity with particular deterioration in the later decades of life.

Aging

The deteriorative effects of aging per se certainly have the potential to affect the development of muscle weakness through accumulation of metabolic debris as cross linkages, membrane stiffening, and DNA alteration. But the facts that not all old people demonstrate muscle wasting and that it is clearly reversible cast doubt on the degree of the participation of aging per se in the production of frailty (20,33).

Rate of Change

It is likely that the body's maximum functional capacity exists around the time of cessation of body growth, approximately age 30. For the adult, reserve capability constitutes the baseline against which further deficits are drawn. Ferrucci and colleagues observed that the course of frailty in young and old is basically different (68). Whereas in the young, the onset of the frail state is usually quite abrupt, in older persons, it is more attenuated. An extensive review of 445 studies in 13 systems, including muscle strength and $\dot{V}O_2$ max, confirms that 0.5% per year is the median rate of deterioration of many functions in normal persons (69,70). However, this rate is subject to marked alteration with regard to muscle strength. Martin and colleagues recently reported that muscle power declined at the average rate of 0.75% per year in a group of competitive cyclists (71). A casted limb or an individual at bedrest has been shown to exhibit a decrease in muscle strength at the rate of 1% per day, at least during a 70-day observation period (72). The

rate of $\dot{V}O_2$ max loss shows parallel declines that are exercise dependent (73).

Evans has urged that muscle power is a more discriminate assessment of muscle function than is strength alone in as much as it includes speed as well as strength within its definition (74). Foldvari and colleagues recently showed that in a group of older women, average age 74.8, who are identified as at high risk of frailty, leg power was the most highly correlated of all measurements to functional state (75), including clinical diagnosis and medication use.

Skelton and colleagues showed that in 65- to 89-year-old healthy men and women, hand grip and quadriceps strength declined 1.5% per year, whereas leg power declined 3.5% per year (76). This formulation proposes that frailty is evident by the loss of 70% of basal muscle power. It is clear that the rate of its development is highly dependent on the degree of inactivity that provokes it. The variance in the rate of change, which in turn is dependent on different inputs, prominently lifestyle, is a predominant cause of the often-described heterogeneity of older persons, more than genetic variance, illness and injuries, and the rate of aging. Further, Kosaka and colleagues observed the mean survival of older persons upon becoming bedridden is 1.8 years (77).

Diagnosis

Numerous criteria have been proposed for the diagnosis of frailty in relation to the causative mechanisms described above. Some, such as the APACHE and LOD systems, employ multiple organ system abnormalities to produce their scoring criteria (78,79). Closer to this proposed definition of frailty, however, are other measurement systems, such as the geriatric status scale (GSS), the Barthel index, and PULSES profile, all of which predominantly utilize strength and mobility indexes in their schemes (80). Fried and colleagues recently proposed a five-item index—weight loss, lack of exercise, grip strength, walking speed, and fatigue—for the prediction of the frailty phenotype (3). Reporting on the results of the important Ficsit study, Ory and colleagues described frailty as a state characterized by severely impaired muscle strength, mobility, balance, and endurance (19). These characterizations focus attention on compromise of locomotor competence as the gateway defect leading to frailty and its systemic implications.

Prevention and Treatment

Numerous studies have demonstrated the predictive value of muscle weakness with regard to total mortality (81). This prediction holds even for older persons confronting acute illness (82). In a group of middle-aged Japanese men, the stronger half showed one half the mortality rate of the weaker half during a 6-year observation (83). Rantanen and colleagues reported that muscle grip strength measured in healthy 45- to 68-year-olds predicted all-cause mortality risk regardless of body mass index over a 30-year follow-up period (84). Earlier, Blair and colleagues showed an increasing age effect on the inverse relationship of physical fitness to all-cause mortality (85).

Although frailty, itself, is not generally considered a fatal illness, its corollary deteriorations in other organ systems certify it as a state of increased risk of death. Acceptance of the proposition that the state of frailty is keyed by muscle weakness leads directly to the simple preventive and remedial strategy of physical exercise. This advisory has been repeatedly given (86). Its embrace is cheap, effective, universally available, and without significant side effects. Because muscle weakness, as frailty, has been identified as having strong predictive values for disability, institutionalization, and death, as well as many clinical correlates, it makes sense to propose that some muscle competence measurement be included in the basic battery of patient evaluations. A simple muscular test, if routinely used, should prove of great prognostic clinical value, possibly more than the standard pulse, respiration, temperature, and blood pressure readings. Perhaps leg power is a more "vital" sign.

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Address correspondence to Walter M. Bortz, MD, 167 Bolivar Lane, Portola Valley, CA 94028. E-mail: drwbortz@aol.com

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