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Review

Frailty: A Vital Sign for Older Adults With Cardiovascular Disease

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ABSTRACT

Mechanisms of aging predispose to cardiovascular disease (CVD), as well as to aggregate health challenges. For older adults, CVD is likely to exist in combination with comorbid conditions, disability, polypharmacy, falling risks, and body composition changes. These other dimensions of health result in cumulative weakening with greater clinical complexity that confound basic precepts of CVD presentation, prognosis, and treatments. A convenient operational tool is needed to gauge this age-related vulnerability such that it can be integrated in the evaluation and treatment of CVD. Frailty is a concept that is neither disease- nor age-specific, but is used to characterize the reserve that a person has available to tolerate stresses associated with aging, disease, and even therapy. Frailty arises from specific biological mechanisms in association with cumulative physiological decrements, psychosocial stresses, and physical impairments. Performance-based and survey tools have been developed and tested to measure frailty. Although different frailty tools vary in practicality, measured domains, and precise applications, all are useful in identifying risks that

RÉSUMÉ

Les mécanismes du vieillissement prédisposent aux maladies cardiovasculaires (MCV) ainsi qu'à l'ensemble des problèmes de santé. Chez les personnes âgées, il est probable que les MCV existent en association avec des états comorbides, une incapacité, une polypharmacie, des risques de chute et des changements dans la constitution corporelle. Ces autres dimensions de la santé entraînent une diminution cumulative d'une complexité clinique accrue qui va à l'encontre des préceptes fondamentaux du tableau clinique, du pronostic et des traitements des MCV. Un outil efficace pratique est nécessaire pour mesurer cette vulnérabilité liée à l'âge de manière à ce qu'il puisse être intégré à l'évaluation et au traitement des MCV. La fragilité est un concept qui n'est ni lié à la maladie ni lié à l'âge, mais il est utilisé pour définir la réserve disponible de la personne pour tolérer les stress associés au vieillissement, à la maladie, voire au traitement. La fragilité résulte de mécanismes biologiques précis en association avec la diminution cumulative des réserves physiologiques, le stress psychosocial et la détérioration physique. Des outils axés sur la per-

Although a precise criteria for frailty is often debated, the term generally implies a state of vulnerability to stressors and limited reserves to stabilize declines across multiple physiologic systems.[1] A vital sign typically refers to measurements that indicate the state of a person's general physical condition. As the population of older adults expands, it becomes progressively important to integrate frailty as a vital sign in older adults to guide management and coordinate better care. Adults who are frail are prone to developing disease, and have worse disease outcomes and greater risks for harmful sequelae from standard therapies. Nevertheless, the theoretical appeal of frailty as a vital sign remains encumbered by ambiguity regarding the standardization and application of the concept. Ongoing debate about frailty as a phenotype or as deficit accumulation further obscures its implementation in the clinic setting.

Frailty has been prominent in the geriatric literature for years, but recently surged as a topic for cardiovascular (CV) clinicians and researchers (Fig. 1).[2] To a large extent, the expanding demographic of older adults is driving the need for better benchmarks of aging than chronologic age alone. By 2030, 20% of the United States population will be older than 65 years, with higher proportions thereafter, and the subset of adults aged 85 years and older is increasing the most rapidly.[3] Incidence of frailty increases with age as does CV disease (CVD), making their coexistence common.[4] Even frail individuals without known CVD are more likely to have more CV risk factors than individuals who are not frail.[5] Health care standards have evolved to place greater emphasis on "value of care"[6] and patient satisfaction, yet frail patients are more likely to experience suboptimal outcomes despite flawlessly executed procedures and/or precisely administered medications. Amidst these challenges, a routine, standardized measure of frailty

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commonly accrue with age. Although comparisons between frailty tools are ongoing and sometimes even controversial, the rationale to integrate routine use of frailty screening as part of routine care is relatively straightforward and easy to envision. Frailty assessment applied as a vital sign (for standard maintenance and evaluation of new symptoms) enhances perspectives of risk, decision-making, and opportunities for tailored CVD management.

formance et des outils d'enquête ont été élaborés et testés pour mesurer la fragilité. Bien que les différents outils de mesure de la fragilité varient dans la pratique, les domaines mesurés et les applications précises, tous sont utiles pour déterminer les risques qui augmentent fréquemment avec l'âge. Bien que des comparaisons entre les outils de mesure de la fragilité soient en cours, même s'ils suscitent parfois la controverse, les raisons d'intégrer l'utilisation systématique du dépistage de la fragilité dans le cadre des soins courants sont relativement simples et faciles à concevoir. L'évaluation de la fragilité utilisée comme signe vital (pour le maintien normal et l'évaluation des nouveaux symptômes) améliore les perspectives du risque, la prise de décision et les possibilités d'adaptation de la prise en charge des MCV.

could help guide management decisions as well as tailored therapeutic strategies that optimize care and outcomes.

Linkages Between Frailty and CVD

Frailty occurs when oxidative stress, cell senescence, and mitochondrial damage reach a tipping point in the balance between cellular injury and repair.[7] Genetics and environmental stress determine the tipping point for each individual[8], which is heralded by inflammation (Fig. 2).[9] Frailty and CVD both arise from activated inflammatory pathways with adverse biological effects.[7] As noted in the Alameda study[10], the same risk factors that predispose to frailty (eg, obesity, smoking, sedentary lifestyle) are also CV risk factors, because increased allostatic load (ie, physiological consequences of accumulated exposure to neurohormonal activation from repeated or chronic stress) increases the risks of both.[10,11] Inflammation triggers oxidation of lipoproteins and destabilization of plaques, increasing risk of CV events.[12] Inflammation also promotes a catabolic state that triggers altered patterns of gene expression and associated physiological changes.[13] Physiologic changes from this process includes a redistribution of amino acids from skeletal muscle to other organs.[14] The resulting loss of muscle mass and change in muscle metabolism impairs the body's ability to maintain and repair itself in the face of stressors.[15] The changes in body composition are compounded by the tendencies of inflammation and neurohormonal dysregulation to also lessen activity and appetite, further decreasing activity.[16] Circulating inflammatory biomarker levels (high-sensitivity C-reactive protein and interleukin-6), as well as inflammatory cells (neutrophils and monocytes) are increased,[17] as are levels of downstream thrombotic markers such as factor VIII and D-dimers in both conditions.[7] Inflammatory mechanisms trigger other diseases as well as contribute to the advent of frailty, so CVD and frailty often coexist with multimorbidity.[18]

Frailty as a Contemporary CV Issue

Incorporating health priorities near the end of life have long been a part of decision-making for patients who undergo certain cardiac procedures.[19-21] However, the advent of transcatheter aortic valve replacement (TAVR) intensified interest in frailty more broadly. Aortic stenosis increases with age, but for years the only option for severe aortic stenosis was a surgical aortic valve replacement. Patients were routinely screened using the ambiguous "eyeball test"[22] to determine if they were sufficiently robust for the life-saving surgery. With the advent of TAVR, frailty became a key selection criterion for use of TAVR, and the validity, reproducibility, and specificity of the "eyeball test" came into question. Gradients of frailty also became relevant to select frail patients who would most benefit.[23] Interest in frailty was soon shared by other CV providers as a perspective with which to better achieve personalized management with respect to acute coronary syndromes,[24,25] coronary heart disease,[26] and revascularization,[27,28] aortic valve replacement,[28,29] implanted cardioverter defibrillators,[30] heart failure,[31,32] and medications.[33] Value-based health care, shared decision-making,[34] and palliative care[35] reinforced application of frailty as a way to better conceptualize discussion of desired outcomes.

The Frailty Phenotype vs the Frailty Index

In the geriatric literature, a single frailty tool has not become dominant.[36] However, 2 prevailing approaches to identify frailty have evolved (ie, frailty conceptualized as a phenotype vs frailty conceptualized as an index). A phenotype describes a set of observable characteristics, and an index is more of a numerical construct. The historical "eyeball test" for frailty assesses a frailty phenotype as the observer selects from a

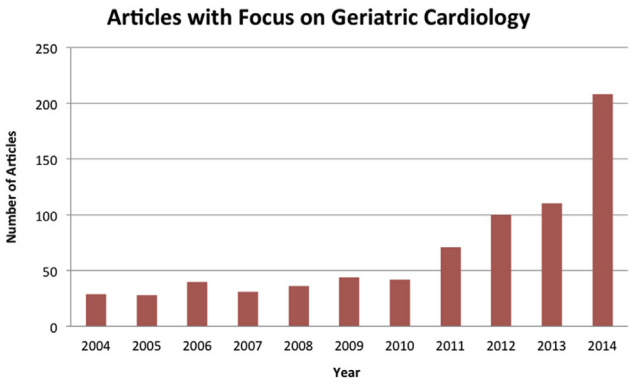

Figure 1. PubMed citations for geriatrics and cardiovascular disease from 2006 to 2015. Dodson et al.[2] show a proliferation of citations linking geriatrics and cardiovascular disease, including a heavy emphasis on the pertinence of frailty. Reproduced from Dodson et al.[2] with permission from Elsevier.

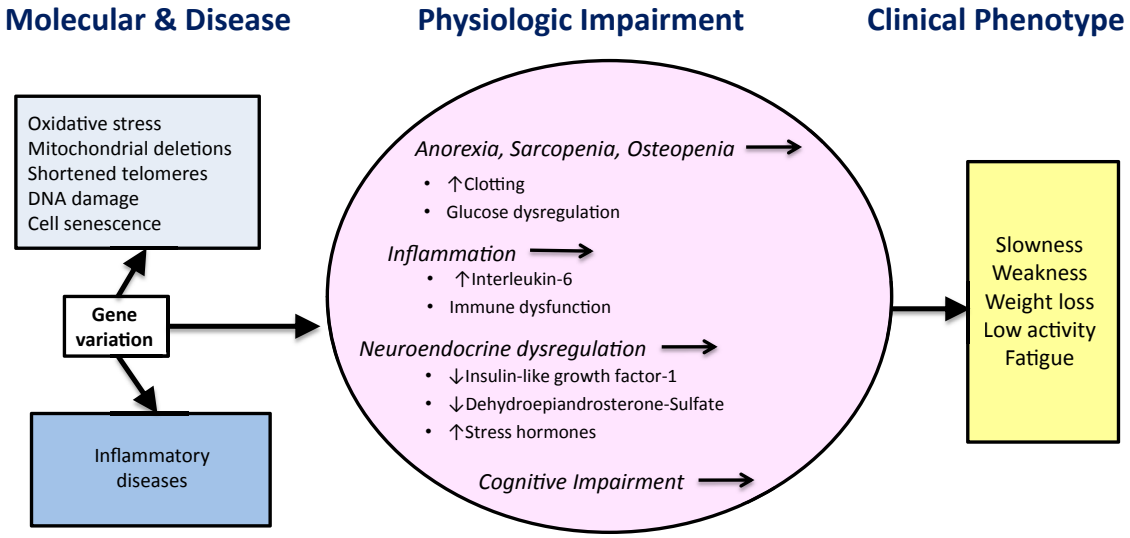

Figure 2. Pathophysiology of frailty. Walston et al. completed seminal work showing the biologic underpinnings of frailty, and the overlap with mechanisms also pertaining to cardiovascular disease. Modified from Walston et al.[9] with permission from John Wiley and Sons.

set of characteristics regarded as important by that observer on the basis of their view of the phenotype. Therefore, to distinguish frailty more precisely the quantification of specific domains (eg, slowness, fatigue, weakness, nutritional wasting, and low activity) seemed consistent and logical to many. Therefore, the validated Fried frailty phenotype, which defines 5 key domains for frailty: weakness, low energy, slowed walking speed, decreased physical activity, and weight loss quickly garnered attention in the CV community.[1] Fried's frailty score is on the basis of an integrated biological perspective, without focus on a single aspect of decline but the overall context of homeostasis. Fried differentiated frailty from multimorbidity and disability, articulating that frailty predisposed to the other conditions, but frailty was a distinct biologic syndrome.[18] Those with impairment in 3 or more of the 5 domains are frail. Some have integrated impaired cognition[37] and depression[38] to complement the phenotype. Such modification is arguably useful with respect to achieving greater diagnostic and prognostic sensitivity, but also problematic with respect to the fundamental inconsistency of assessment. In addition, the original Fried score used some longer survey instruments that have subsequently been modified for convenience and brevity, which threatens standardization. Nonetheless, the Fried phenotype remains conceptually compelling to many, especially on the basis of evolving insights regarding the role of inflammation that were becoming widely discussed over the same period.

An alternate tool to identify frailty, attributed to Kenneth Rockwood, conceptualizes frailty in terms of the numeric count of deficits.[39] Rockwood conceptualizes frailty as an amalgamation that includes disability and multimorbidity. He developed the notion of a frailty index that is calculated as a ratio derived from a large number of clinically relevant candidate variables (ie, the number of deficits relative to the number of domains assessed). Rockwood's premise is that as many candidate variables as possible should be assessed, with reliability of a frailty assessment being greater as the numbers of assessments increases. Essentially, he describes aging as a stochastic framework that links deficit accumulation to the interaction between environment and the organism.[40] The speed and magnitude of deficit[40] accumulation characterizes key aspects of aging. Although Rockwood originally identified 92 candidate domains to assess the frailty index,[41] he then determined that as few as 30 provide sufficient resolution for effective measurement.[42] Whereas such refinement was primarily intended to improve convenience and applicability (and also to respond to criticisms that the index was too unwieldy), it also created problematic variability of assessment. Despite such intricacies, Rockwood still asserts the overall value of the frailty index in terms of its capacity to distinguish frailty more sensitively than a simple phenotype score because it includes relatively more variables to characterize the principle of deficit accumulation, including disability and multimorbidity.[43] Despite conceptual differences, Fried and Rockwood, and the many other contributors to this literature, similarly depict frailty as a state of increased vulnerability, and describe consequences attributable to its presence.

Ease of implementation and clinical utility is often considered an important distinction between the 2 dominant frailty models. The Fried score is usually considered easier to implement in the clinic. Alternatively, Rockwood's index is considered by many to be particularly valuable in relation to data sets.[44] Recent work in Olmstead County using the Rockwood index, combining body mass index, 17 comorbidities, and 14 activities of daily living, supported the notion of mapping of trajectories of frailty at the population level.[45] Furthermore, the Rockwood index has been modified multiple times with the rationale that its applicability can be enhanced without undermining the basic principle and value of the assessment.[40]

Alternatives to these dominant frailty scales include assessment using single performance measures like gait speed, Timed Get up and Go,[46] chair stand test,[47] or hand grip strength.[48] Such performance measures provide relatively easy screening and assessment, which resonates with the frailty phenotype. The prognostic utility of gait speed in community populations provides compelling validation as a single assessment of physical

frailty.[25,49,50] The continuous nature of gait speed also enables detection of small changes (0.1 m/s) where ordinal scales might not be as sensitive.[51,52] Simple performance measures other than gait speed (eg, Timed Get up and Go, Short Physical Performance Battery) are also easy to implement.[22,46,51,53] However, all these performance assessments are criticized for lack of specificity. Deconditioning, disease, or musculoskeletal impediments that have nothing to do with frailty might affect their results. Numerous studies and reviews have described the tension between frailty assessments that are parsimonious and relatively more convenient vs assessments that entail multiple indices (ie, relatively more difficult to perform but also relatively more specific and reliable).

Advancing the Concept of the Vital Sign

Guidelines acknowledge the importance of patient-centred approaches with consideration of frailty.[54] However, frailty's multiple dimensions and dynamic nature are likely to make a single classification elusive. The variety of tools illustrates spectrum of vulnerability that can be classified, and frailty is associated with worse prognosis across all assessment methods. In fact, there might never be a gold standard, but use of any tool is better than omission of this perspective. Therefore, the selection of a specific scale or performance measure might depend on the intended purpose. An analogy might be the various formulas for calculation of the estimated glomerular filtration rate; the Cockroft-Gault equation and the Modification of Diet in Renal Disease equations are different, but each provides classification of renal function beyond serum creatinine.[55] Just as estimated glomerular filtration rate calculations vary but achieve similar value, frailty screens also vary, but each advances classification beyond age alone.

Because of the need for brevity in the clinical setting and befitting of a vital sign, comprehensive frailty assessments are unlikely to be adopted. One consideration to achieve an optimal balance between feasibility and specificity of assessment is to have a 2-tiered approach to frailty assessment. Simple proxies of frailty on the basis of gait speed, Clinical Frail Scale,[56] or **F**atigue, **R**esistance (ability to climb 1 flight of stairs), **A**mbulation (ability to walk 1 block), **I**llnesses (greater than 5), Loss of Weight (> 5%) (FRAIL) score[57] do not provide specificity of more comprehensive assessments, but they do provide a standardized minimum assessment that is sensitive for impairment and realistic. Just as with the Patient Health Questionnaire-2 (PHQ-2)[58] for depression, abnormal responses can lead to further investigation. The standardization of the assessment should also be encouraged within each care environment on the basis of local preferences.

Frailty is also a dynamic concept. Just as renal function is assessed recurrently as a dynamic function that can change over time, a repeated measure of frailty performed at intervals can be used to identify new changes in a vital status. If adopted as a vital sign, widely and serially assessed frailty indicators would provide valuable normative perspectives such that even small changes could prompt investigation.[59] Patients identified as prefrail are at risk for future functional decline and development of incident CVD.[60] Thus, longitudinal assessments could better detect early stages of frailty to better focus on prevention.

Future Directions

Classifying frail patients in clinical research and practice will advance our ability to best care for these patients. An abundant literature reflects a surge of candidate tools, on the basis of the frailty phenotype or the frailty index, and many variations on these tailored to different clinical contexts.[61-65] It is beyond the scope of this brief account to review this literature, but rather to highlight its magnitude and sense of importance. Even as methodological issues remain, frailty testing might prompt discussions about aging, vulnerability, and adverse outcomes, inviting patients to discuss priorities and preferences. Likewise, frailty assessment might provide a critical opportunity to modify procedures, medications, and the process of care to optimize outcomes and efficacies of care. The progression from frailty to disability and death might also be modifiable if identified early (Fig. 3).[66] Prehabilitation before surgery,[67] and rehabilitation[68] after surgery enable focused attention of strength, and modifications of the environment. With the underuse of cardiac rehabilitation specifically in those at greatest risk, other home-based interventions are needed.[69,70] Interventions such as caloric restriction and metformin target the metabolic drivers of aging.[71,72] Protein supplements replenish critical nutritional deficits.[73] Other interventions early in the process, guided by telomeres or biomarkers, are future visions yet to be realized but might maximize quality of life in later years.

Conclusions

Because most older adults are not frail, age is less important than age-related vulnerability in the older population. While a precise definition and single tool to identify frailty remains elusive, the identification of age-related vulnerability in the routine care of older adults must proceed. Frailty evaluation can be achieved using many different tools, each with distinctive attributes, but similar utility to gauge dimensions of health in older populations distinct from disease. Such assessment is particularly relevant for older CV patients with heterogeneity of aging and multimorbidity. Including frailty as a contemporary vital sign can help evaluate baseline health of older adults, inform the implications of disease management, and optimize strategies to preserve independence.

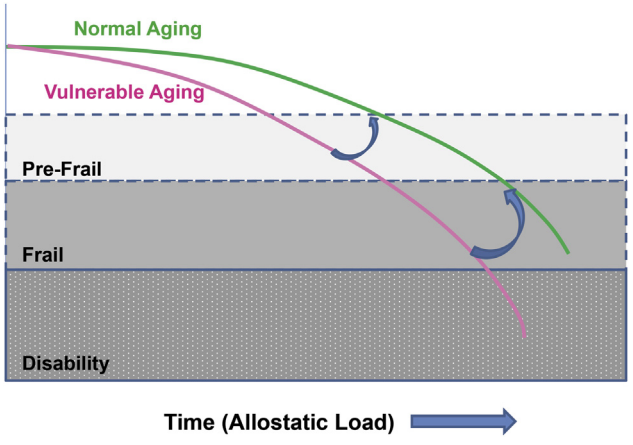

Figure 3. The age-frailty continuum. Abellan van Kan et al. showed the important opportunities for intervention, such that prefrailty and frailty might be modified. Adapted from Abellan van Kan et al.[66] with permission from Springer. © 2008 The Journal of Nutrition, Health and Aging.

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Disclosures

The authors have no conflicts of interest to disclose.

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