Relationships of Cardiac, Pulmonary, and Muscle Reserves and Frailty to Exercise Capacity in Older Women

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Background. A decline in exercise capacity (EC) is a characteristic of frailty. We hypothesized that decline is the effect of decrements in several physiological systems. We assessed whether the relationship of three main physiological systems—cardiac, pulmonary, and musculoskeletal—to EC is independent or interactive and whether their effect on EC varies with respect to frailty status.

Methods. Observational study of 547 disabled women aged 65 years and older (Women’s Health and Aging Study I) including 131 frail who participated in a test of EC. EC (seated step test), cardiac function (chronotropic index), pulmonary function (forced vital capacity, FVC), musculoskeletal function (quadriiceps strength, QS), and frailty status were measured and interactive effects were modeled using linear regression and differentiation.

Results. Each physiological system had a direct relationship with EC, which was lower in frail compared with non-frail. The relationship between FVC and EC was positive and increased with increasing QS in nonfrail subjects. The effect of QS on EC was positive and increased with increasing FVC regardless of frailty. In subjects with low QS, frailty status was associated with lower EC and this effect became stronger with increasing FVC.

Discussion. Findings suggest but do not show that frailty status modifies the effects of physiological function in several systems on EC. Approaches to understanding emergent properties such as vulnerability to illness and death and clinical efforts to prevent and treat frailty should evaluate and possibly intervene on several physiological systems to be maximally effective.

Key Words: Frailty—Exercise capacity.

It has been proposed that frailty, a syndrome of old age, results from an impairment across physiological systems (1) that leads to loss of homeostatic resilience. The hallmarks of this loss of integration of physiological function are increased susceptibility to stressors and even death. Because homeostatic resilience is inherently dynamic, losses are more likely to be unmasked as impaired ability to respond to a stressor than as a change in function under resting conditions. Frailty is thought to manifest a loss of physiological complexity as a qualitative change in the manner, not just a diminished amount, of response to stress via several physiological systems (2). However, this theory remains to be evaluated. Few frail older adults have been tested through stress tests, so the loss of function that would be evident from studying interactions among physiological systems under stress remains largely theoretical (3).

A clinical phenotypic or operational definition of physical frailty composed of several components among weakness, slowness, low activity, exhaustion, and weight loss has been shown to have construct and predictive validity as evidenced by its association with increased risk of future physical disability and death (4) and discriminant validity as a syndrome (5). Although frailty is thought to result from functional decline in several systems, including immunologic, hormonal, and neural (6,7), a central feature embedded in the frailty criteria is lower extremity exercise capacity (EC). We hypothesized that the systems involved in converting energy into lower extremity EC interact, that is, respond differently to each other in frail adults compared with non-frail adults. Identifying a difference in integrated function according to frailty status would contribute in previously unexplained ways to our current understanding of EC in late life.

This study aimed to address these questions by: (a) determining the relationship between key physiological systems and EC in disabled older women, a cohort that provides an opportunity to study frailty but is underrepresented in physiology literature and (b) evaluating for interactions among these systems with frailty status with respect to their association with lower extremity EC obtained through a graded...
exercise test. More specifically, we sought to determine the degree to which lower extremity EC was a function of measured central cardiovascular limit, a pulmonary mechanical limit, and/or a limit in peripheral oxygen utilization, whether these functions interacted, and, they were conditioned on frailty.

**METHODS**

**Data**

Data are from the Women’s Health and Aging Study I, a population-based observational study of moderately to severely disabled community-dwelling older women designed to study the causes and course of physical disability (8). The cohort was derived from an age-stratified random sample of 32,538 female Medicare recipients aged 65 years and older living in eastern Baltimore City and County. Inclusion criteria were both of the following: self-report of difficulty or dependence with tasks in two or more of the following four functional systems: mobility, upper extremity, higher functioning tasks, and self-care tasks; and second, Mini-Mental State Examination (MMSE) (9) score greater than or equal to 18. A total of 1,002 women enrolled. All research staff received extensive training to ensure standardization of techniques, which have been described previously in detail (10). The Johns Hopkins Medicine Institutional Review Board approved the study.

**Outcome: EC**

Baseline examination included a low-level graded exercise test (the seated step test, SST) (11,12), with the following exclusion criteria: chart review disclosing aortic valve stenosis, myocardial infarction within the last 6 months, unstable angina, severe pain in hip or knee; evaluation finding acute infection, rales on auscultation of the lungs or dyspnea, loud systolic murmur, resting diastolic blood pressure more than 100 mmHg or systolic blood pressure more than 200 mmHg, or pulse more than 75% maximum predicted heart rate; or electrocardiogram showing arrhythmia. The SST has four 3-minute stages (2.3, 2.9, 3.5, and 3.9 metabolic equivalents [METs]) during which participants performed a steplike motion while seated in a chair. A step 6 inches tall was placed at a distance determined by the heel of the extended leg. Step heights were increased for stages 2 (12 in) and 3 (18 in), and for stage 4, participants were also asked to lift the arm in a position parallel with the stepping leg. Participants were instructed to step to the count of a metronome set for 1-second beats, placing the arch of each foot on the step. EC was measured as the exercise time completed. Stopping criteria for the test included reporting chest pain, lightheadedness or dizziness, shortness of breath, or inability to go on; systolic blood pressure >200 or <90 mmHg, diastolic blood pressure >100 mmHg or <60 mmHg, oxygen saturation ≤80%, or pulse >75% predicted maximum; electrocardiogram evidence of >3 premature ventricular contractions in 30 seconds, QRS complex widening to >3 mm, or, ST segment depression >1 mm.

**Predictors: Cardiac Chronotropic Index, Forced Vital Capacity, Quadriceps Strength, and Frailty Status**

Given the objective of examining interactive effects, the parameter with the strongest association with EC for each system was used. Four cardiac measures were evaluated: heart rate reserve (difference between the lowest pulse and pulse when stopped test); rate–pressure product for each stage (pulse × systolic blood pressure); heart rate recovery (time to return pulse to <100); and chronotropic index (CI) for each stage (13) [(metabolic reserve/heart rate reserve = ((MET_{stage}−MET_{rest})/(MET_{peak}−MET_{rest}))/(HR_{stage}−HR_{rest}))/((220−age in years − HR_{rest})], where MET_{stage} was derived from SST literature values (11) and MET_{rest} was derived from predictive equations] (14). A significant association with EC was found only for CI. Two pulmonary measures were considered: forced expiratory volume in first second (FEV1) and forced vital capacity (FVC) were measured following Epidemiology Standardization Project and American Thoracic Society guidelines. The association with EC was stronger for FVC. Quadriceps strength (QS) was measured using a handheld dynamometer using the best reading from two trials of each leg (12). Frailty status was determined using previously validated criteria (4) as the presence of at least three of the following five: usual walking speed ≤0.65 m/s if height ≤159 cm or ≤0.76 m/s if >159 cm; grip strength ≤17 kg for body mass index (BMI) ≤23 kg/m², ≤17.3 kg for 23.1–26 kg/m², ≤18 kg for 26.1–29 kg/m², or ≤21 kg for >29 kg/m² using a grip hand dynamometer; reporting <90 kcal/d of activity; reporting low usual energy or feeling unusually tired or weak; weight loss of ≥10% since age 60 years or BMI <18.5 kg/m².

**Potential Confounders**

Demographic and health status variables were carefully measured for the source population of disabled older women, including the subsample who participated in exercise testing. Demographic variables included age, years of education, and race. Health status indicators included adjudicated prevalent disease based on review of medical records (12), medications including beta-adrenergic receptor blocking and non-dihydropyridine calcium channel blocking agents, MMSE score, and Geriatric Depression Scale score (15).

**Analytic Methods**

Exploratory data analysis revealed that the outcome fits a normal distribution after log transformation better than a Poisson or negative binomial distribution, so linear regression was employed. Scatter plots were used to inspect for outliers. Simple, linear pairwise interaction regression models in which all parameters depend on each other
(Y = β₀ + β₁x₁ + β₂x₂ + β₃x₃ + β₁x₁x₂ + β₂x₁x₃ + β₃x₂x₃ + ε) and fully interactive models (pairwise + β₁x₁x₂x₃) were compared using hypothesis testing and adjusted $R^2$, Akaike Information Criteria, and Bayesian Information Criteria. Standard errors were drawn from the variance–covariance matrix. To simplify the presentation of interactions occurring in three dimensions, the effects were displayed one at a time across clinically meaningful values of the other parameters, with 90% confidence intervals instead of 95% following convention for interactions (16). The potential for exclusion criteria to bias inferences was assessed by comparing the propensity for frailty according to test participation using propensity score methods (17). Stata Special Edition version 9.2 (StataCorp, College Station, TX) statistical software was used for the earlier analyses. In addition, two analyses were conducted to detect nonlinear interactions and model misspecification: recursive partitioning (18) and statistical boosting (19). These analyses were performed in R version 2.4.1 (R Foundation for Statistical Computing, Vienna, Austria) statistical software.

**RESULTS**

Table 1 displays sociodemographic and disease characteristics and measures of cardiac, pulmonary, and muscle organ system function overall and, among the women eligible for the SST, by frailty status. For most characteristics, including age, years of education, race, BMI, chronic disease count, arthritis, MMSE score, and Geriatric Depression Scale score, the mean or the proportion in the population (first column) lay between values for non-frail and frail women tested (2nd and 3rd columns). There was a lower proportion of coronary artery disease, congestive heart failure, and taking pulse-blocking medications and a higher proportion with chronic lung disease in the tested subgroup. The distribution of EC was shifted to the left (lower) in frail women and is displayed in Figure 2. Of the 131 frail women who participated in the SST, 67.2% had a propensity to participate of less than 0.50 and were therefore representative of women who did not participate in the SST (Figure 1). A pulse greater than 75% predicted maximum was the reason for stopping the exercise test in only 8.8% of cases, and no meaningful differences in test stopping criteria were observed between frail and non-frail.

The direct relationships between the three systems of interest and EC, stratified by frailty status, are displayed using scatter plots and linear fit lines in Figure 3A–C. As expected, lower EC was associated with a higher CI and lower FVC and QS on average ($p$ values from $t$ tests of sample means with
unequal variances were .012, <.001, and <.001, respectively).
For all three systems, EC was lower in frail compared with non-frail.

Table 2 displays the noninteractive model and final interactive model to evaluate the relationships between key physiological systems and EC in disabled older women in the sample. In the noninteractive model, all measures were significantly associated with the outcome with the exception of CI, which achieved borderline significance. Model building with hypothesis tests and comparisons of model fit resulted in CI being dropped as a predictor in the final model (the $p$ value from the hypothesis test for the contribution of CI in pairwise chained model as described in the Methods section was .209), consistent with its weaker association with the outcome and absence of interaction with frailty observed in the preparatory and exploratory steps earlier. In the final interactive model, EC was associated with FVC and QS in a positive manner and with frailty in a negative manner. Each term in this traditional presentation of model results is merely the effect when all other variables are 0; thus, the full interactive results follow graphically.

The research questions addressed graphically in Figure 4A–C were to understand how each system’s effect on EC varied according to the status of the other system and

Figure 1. Propensity to be frail, according to participation in the seated step test of exercise capacity.

Figure 2. Distribution of exercise capacity (minutes of seated step test completed) according to frailty status in moderately to severely disabled older women.

Figure 3. Associations of chronotropic index (CI), forced vital capacity (FVC) and quadriceps strength (QS) with Exercise Capacity, according to frailty status.
frailty. Three questions can be asked from each section of the figure: whether the effect is nonzero (90% CI bands crosses the zero line); whether the effect is positive or negative and changes with values of the second parameter; and whether the effect differs according to levels of the third parameter (open vs closed circles). In Figure 4A, the association of FVC with EC was significantly positive at QS more than 10 kg and only for non-frail older women. The effect of QS on FVC’s effect was positive (upward slope). In frail subjects, FVC level had no significant effect on EC (overlap with 0 at all levels of QS). In Figure 4B, the effect of QS on EC was significantly positive across levels of FVC for both non-frail and frail subjects and increased with increasing FVC in a synergistic manner. Figure 4C shows how the association of frailty status with EC was significantly negative in participants whose leg were weak, but not in those whose legs were strong. This negative association became stronger with higher FVC. Overall, though significant effects occur at the levels noted earlier, the three-way interactions are not statistically significant, as indicated by the overlap of the 90% confidence bands at low and high values of the second and third parameters. To assess whether differences in trunk height could have biased our results, we re-ran the analyses using percentage-predicted FVC instead of FVC, where predicted FVC came from Knudson’s formula, and found no substantial deviation from our findings.

**DISCUSSION**

The findings from this community-based cohort study suggest that key physiological impairments in lung function and leg strength and frailty cause diminished EC linearly and cumulatively in disabled older women. Furthermore, and more specifically, we found that the positive effects of pulmonary function on EC were significant only in the absence of frailty but were muted in frailty, a finding that suggests integrated functioning may become degraded or uncoupled in frailty. We failed to find significant differences in the linear interactive effects of pulmonary function and leg strength on EC according to frailty status. Therefore, frailty status may represent an important indicator of higher order physiological integrity, but the data here do not support the notion that frailty modulates these physiological systems markedly. By examining interactions in three dimensions, we provide evidence that at some level of accumulated impairments integrated functioning such as EC may be strongly affected.

This study provides evidence regarding the interactions among physiological systems required to perform lower extremity work and provides insights on the interrelationships of key physiological systems that appear to merit further testing. In particular, this study extends previous research on the importance of lung function to EC (20–22) and lower extremity strength (23) for EC to an understudied older population, women living in the community with disability. Because changes in health status in later life often result from several factors impinging on more than one system, the likelihood that a clinical intervention will achieve positive results increases with the number of systems the intervention affects positively (24). This suggests that this may be particularly to those who are frail. An intervention designed to improve both pulmonary function and leg strength may be much more effective on EC outcomes than one designed to improve either alone (25). The evidence presented here extends this prior work to suggest
that an intervention designed to improve both pulmonary function and leg strength may be much more effective for EC outcomes than an intervention that improves either type of function alone because loss of physiological reserves occurred in several systems. Thus, frailty may result from a convergence of disease or aging effects. Sarcopenia may be a final common pathway causing respiratory muscle weakness that manifests as loss of pulmonary function and leg strength. A convergent pathway, if it exists, is likely to consist of a complex web of directly- and indirectly-related physiological impairments. For example, vitamin D deficiency may have diverging effects in the form of sarcopenia and osteoporosis, which can in turn contribute to thoracic kyphosis and impaired pulmonary function. It is unlikely that many cases of frailty can be explained by a single type of pathology. In addition, it may be that the most ameliorable physiological changes occur before the development of full-blown frailty.

We found that conducting this research within an observational study of the one-third most disabled older women was feasible and provided heterogeneity to examine interactive effects in free-living humans. Such effects are difficult to identify in small samples due to the correlated variance inherent to interactions. We were able to delineate how the study sample overlaps with the reference population in characteristics related to the measures of interest. This is important because it allowed us to describe selection effects and the potential applicability of the findings to the overall sample to community-dwelling older women.

Several limitations should be considered in interpreting these findings. First, these findings are drawn from disabled older women and therefore await comparison with higher functioning samples of different ages and men. Although the three parameters and the outcome of interest were assessed at the same home visit, not all the measurements were made during actual EC testing. This may have dampened our ability to assess physiological interactions. FVC and QS were measured during brief tests of maximal effort. Although the larger sample size of this study permits considering systems interactions that could not be studied in small samples, while also offering more generalizability, performing data collection in the home limits what can be measured. Heightened safety concerns in a vulnerable older population and cost considerations made more invasive or sophisticated measures of pulmonary function and quadriceps muscle function during an exercise test in participants’ homes not feasible. These limitations would be unlikely to introduce a systematic bias that would explain these results. It is important to consider several possible reasons why heart function was not a significant predictor. The exclusion criteria had the effect of creating a study sample with significantly less congestive heart failure than the full population, raising the possibility of loss of variability and dilution of effect size. In addition, the study participants with congestive heart failure were significantly more likely to be frail, raising the possibility that by forcing frailty into the models, we partially adjusted for impaired cardiac function. Therefore, despite other research also suggesting the primacy of other physiological systems over cardiac function in determining EC...
(20), we contend it would be premature to suggest that heart function is less important than FVC, QS, or frailty with regard to EC in older women. For lung function, we were unable to obtain a full set of measures, such as maximum voluntary ventilation, postural FVC, and respiratory muscle pressures that would be ideal for characterizing lung function. Equipment considerations related to making home visits and the total burden of the protocol on participants made trade-offs necessary. Finally, we note that the absence in this study of measures of two of the traditional compartments of exercise physiology, pulmonary blood flow and peripheral oxygen distribution, comprise important limitations. Measurement of these compartments requires more invasive testing that remains to be performed in a cohort study of older adults.

In summary, this study used an integrated epidemiological, clinical, and physiological theory and demonstrated that in a community-dwelling disabled older women, the relationships of pulmonary function, leg strength, and frailty to EC may be interdependent. Overall, these findings suggest that pulmonary function, leg strength, and frailty may interact to create EC. This suggests that approaches to understanding emergent properties such as vulnerability to illness and death and clinical efforts to prevent and treat frailty should address several physiological systems to be maximally effective.

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