Mechanisms of Ageing and Development 129 (2008) 625–631

Contents lists available at ScienceDirect

Mechanisms of Ageing and Development

journal homepage: www.elsevier.com/locate/mechagedev

Pulmonary function, muscle strength and mortality in old age

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ARTICLE INFO

Article history:
Received 11 January 2008
Received in revised form 15 May 2008
Accepted 25 July 2008
Available online 6 August 2008

Keywords:
Muscle strength
Respiratory muscle strength
Pulmonary function
Mortality
Aging

ABSTRACT

Numerous reports have linked extremity muscle strength with mortality but the mechanism underlying this association is not known. We used data from 960 older persons without dementia participating in the Rush Memory and Aging Project to test two sequential hypotheses: first, that extremity muscle strength is a surrogate for respiratory muscle strength, and second, that the association of respiratory muscle strength with mortality is mediated by pulmonary function. In a series of proportional hazards models, we first demonstrated that the association of extremity muscle strength with mortality was no longer significant after including a term for respiratory muscle strength, controlling for age, sex, education, and body mass index. Next, the association of respiratory muscle strength with mortality was attenuated by more than 50% and no longer significant after including a term for pulmonary function. The findings were unchanged after controlling for cognitive function, parkinsonian signs, physical frailty, balance, physical activity, possible COPD, use of pulmonary medications, vascular risk factors including smoking, chronic vascular diseases, musculoskeletal joint pain, and history of falls. Overall, these findings suggest that pulmonary function may partially account for the association of muscle strength and mortality.

1. Introduction

Numerous studies have reported that extremity muscle strength is associated with an increased risk of death in older persons (Al Snih et al., 2002; Laukkanen et al., 1995; Metter et al., 2002; Newman et al., 2006; Phillips, 1986; Rantanen et al., 2000, 2003; Rolland et al., 2006). However, the mechanisms underlying this association are not known. In some cases, loss of lower extremity muscle strength likely leads to mobility disability, falls, and death (de Rekeneire et al., 2003). However, it is possible that loss of extremity muscle strength may serve as an indicator of systemic disease and represents an early sign of physical frailty, which is associated with mortality (Buchman et al., 2009). A third possibility is that extremity muscle strength is a surrogate for weakness in other skeletal muscles such as respiratory muscles which may be more directly linked to mortality.

Respiratory muscle strength plays a key role in the respiratory network, which depends on intact neural circuitry which orchestrates the interplay between respiratory muscles and intrinsic pulmonary function to maintain adequate ventilation (Kim and Sapienza, 2005; Polkey and Moxham, 2001; Rantanen et al., 2003). In the absence of respiratory muscle activation, pressure gradients cannot be developed and air exchange at the alveolar surface cannot occur. Thus, impaired respiratory muscle strength can lead to pulmonary dysfunction, respiratory distress and even death. Therefore, we hypothesized that extremity muscle strength is a surrogate for respiratory muscle strength, and we also hypothesized that pulmonary function would mediate the association of respiratory muscle strength with mortality. While previous studies have examined the association of extremity muscle strength, respiratory muscle strength, and pulmonary function with mortality separately (Mannino et al., 2003; Sin et al., 2005), we are unaware of any prior study that examined the joint effects of these three indices on risk of death.

We used data from more than 900 older persons without dementia participating in the Rush Memory and Aging Project,

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doi:10.1016/j.mad.2008.07.003

a longitudinal study of common chronic conditions of aging, to investigate the associations of extremity muscle strength, respiratory muscle strength and pulmonary function with mortality (Bennett et al., 2005a). In a series of proportional hazards models, we first tested the hypothesis that extremity muscle strength is a surrogate for respiratory muscle strength. In subsequent models, we tested a second hypothesis that pulmonary function is a step in the causal chain linking respiratory muscle strength to death.

2. Methods

2.1. Participants

All participants are from the Rush Memory and Aging Project, a longitudinal investigation of common chronic conditions of old age (Bennett et al., 2005a). The study was conducted in accordance with the latest version of the Declaration of Helsinki and was approved by the Institutional Review Board of Rush University Medical Center. Clinical evaluations for the study commenced in 1997 but pulmonary function measures were not introduced into the study until 2001. Eligibility for these analyses required the absence of clinical dementia (see below) prior to or at the evaluation when pulmonary function was first obtained as well as a valid extremity muscle strength assessment. We excluded 74 of 1034 potentially eligible participants due to dementia; this resulted in a group of 960 persons eligible for these analyses. Their mean age at baseline was 80.7 years (S.D., 7.4), the mean education was 14.4 years (S.D., 3.0), and the mean Mini-Mental Status Exam score was 28.0 (S.D., 2.1); 74.9% were women and 92.5% were white and non-Hispanic.

2.2. Clinical diagnoses

Clinical diagnoses were made using a multi-step process, as previously described (Bennett et al., 2006). First, subjects underwent detailed annual cognitive function testing which included 21 cognitive performance tests. Second, the cognitive test data were reviewed by an experienced neuropsychologist who determined if cognitive impairment was present. Next, participants were evaluated in person by an experienced neurologist or geriatrician blinded to all previously collected data; this physician then used all available cognitive and clinical testing results from the current years' evaluation to diagnose dementia. A composite measure of cognitive function based on 19 of the tests was used in these analyses. Detailed information about the individual cognitive tests and the construction of the composite cognitive measure are published elsewhere (Bennett et al., 2005a; Wilson et al., 2005).

2.3. Assessment of extremity muscle strength

Muscle strength was measured using portable hand-held dynamometers (Lafayette Manual Muscle Test System, Model 01163, Lafayette, IN). The hand-held dynamometer was used to assess seven muscle groups, including muscle strength in both arms (arm abduction, arm flexion, arm extension) and both lower extremities (hip flexion, knee extension, plantar flexion, and ankle dorsiflexion). In addition, grip and pinch strength were measured bilaterally using the Jamar hydraulic hand and pinch dynamometers (Lafayette Instruments, Lafayette, IN). The mean score for each of the nine muscle groups was converted to a z score, using the baseline mean and standard deviation of all study participants, and the z scores were averaged to yield a composite measure of extremity muscle strength as previously described (Buchman et al., 2007a).

2.4. Assessment of respiratory muscle strength

Muscles needed for adequate respiration include the diaphragm and intercostal muscles which are innervated by cervical and thoracic root segments not involved in limb movements (Kim and Sapienza, 2005). One can isolate and estimate respiratory muscle strength by measuring the maximal pressures generated during inspiration [maximal inspiratory pressures, MIP] and expiration [maximal expiratory pressures, MEP] (Enright et al., 1994; Kim and Sapienza, 2005). A hand-held device that contains a pressure sensitive transducer was used to assess MIP and MEP in cm H_2O [MicroMouth Pressure Meter MP01; MicroMedical Ltd., Kent, UK]. Two trials of both MIP and MEP were measured. The mean score for MIP and MEP were converted to z scores and averaged to yield an overall measure of respiratory muscle strength as previously described (Buchman et al., 2007a).

2.5. Assessment of pulmonary function

Pulmonary function was tested using a hand-held spirometer which measured forced vital capacity (FVC), forced expiratory volume in one second (FEV1) and peak expiratory flow (PEF) [MicroPlus Spirometer MS03, MicroMedical Ltd. Kent, UK] (Otulana et al., 1990). Two trials were collected from each subject. Raw scores from each of the three averaged component pulmonary measures were converted to z scores using the means and standard deviations computed from the entire cohort. A composite pulmonary function score was created by computing the average of the z scores for VC, FEV1, PEF as previously described (Buchman et al., 2007b).

2.6. Mortality

Participation in the Memory and Aging Project includes agreeing to donation of brain, spinal cord, and selected muscles and nerve at the time of death and the study has an autopsy rate of more than 80%. Thus, determination of mortality is most commonly made at the time of death. In the event that autopsy was not successful, additional mechanisms for determining vital status include attempted contact by telephone. At the time of these analyses, 100% of the vital status data were complete and up to date.

2.7. Other covariates

Gender and race were recorded at the baseline interview. Race and ethnicity questions and categories were the same as those used by the 1990 U.S. Census. Age in years was computed from self-reported date of birth and date of the clinical examination at which the muscle strength measures were collected. Education (reported highest grade or years of education) was obtained at the time of the baseline cognitive testing. Weight and height were measured and recorded at each visit by a trained technician blinded to previously collected data. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. We included a term for BMI for linear associations and a quadratic term for BMI (BMI*BMI) because both low and high values of BMI can be associated with adverse health consequences. Physical activity was assessed with questions adapted from the 1985 Health Interview Survey (McPhillips et al., 1989). The times spent participating in each of five physical activities (e.g., walking for exercise), were combined across activities to provide an index of hours of physical activity per week, as previously reported (Bennett et al., 2005a). Parkinsonian signs were based on a modified version of the motor portion of the Unified Parkinson's Disease Rating Scale (Boyle et al., 2005). Balance was based on three lower extremity performances including standing on each leg, standing on their toes and the number of steps off the line when asked to walk heel to toe as previously described (Buchman et al., 2007a). Frailty was based on five components including strength, timed walk, physical activity, BMI and fatigue as described previously (Buchman et al., 2009; Fried et al., 2001). To assess the influence of vascular risk factors and vascular disease burden on the association of motor function and mortality, the number of three vascular risk factors (i.e., the sum of hypertension, diabetes mellitus, and smoking), and four vascular diseases (myocardial infarction, congestive heart failure, claudication, and stroke) were used as covariates in the analyses (Boyle et al., 2005). Falls during the past year and the presence or absence of joint pain were based on participant report (Bennett et al., 2005a). In order to examine the possibility that participants with possible pulmonary disease influenced the results, we considered participants to have possible chronic obstructive pulmonary disease (COPD) if the ratio of FEV1/FVC was <0.7, as suggested by previous literature (Iqbal et al., 2002). In addition, for these analyses, participants who were receiving one or more medications used to treat chronic pulmonary diseases including anticholinergics, beta-adrenergics, theophylline, steroid inhalants, and leukotrienes were considered to have possible pulmonary disease. Medications were inspected and coded using the Medi-Span® system [Medi-Span, Inc.] (Bennett et al., 2005a).

2.8. Data analysis

Pearson (r) correlations were used to assess the relationship of measures of extremity strength and respiratory function with age and education and t-tests to examine sex differences in motor function. We used t-tests or z value of Wilcoxon two sample tests to compare the baseline characteristics of participants who did and did not die during the course of the study.

The first goal of the statistical analyses was to test the hypothesis that extremity muscle strength was a surrogate for respiratory muscle strength in its association with mortality. Therefore, we constructed a Cox proportional hazards model to estimate risk of death associated with extremity strength, controlling for the potential confounding effects of age, sex, education, and BMI. Because education entered as a continuous linear term violated the assumption of proportional hazards, we converted education into a trichotomous categorical measure (0–8 years, 9–12 years and 13 or more years of education) with 0–8 years as the reference category. Because there are known sex differences with respect to muscle strength, we also added an additional term to each of these three models to examine whether there was an interaction with sex. We then added a term for respiratory muscle strength to the model. In these models, losing the effect of extremity muscle strength would suggest that it is a surrogate for respiratory muscle strength.

Next we tested the hypothesis that impaired respiratory muscle strength can lead to pulmonary dysfunction and subsequent death. To do this we conducted a form of mediation analysis. In this case, we first establish a relationship between respiratory muscle strength and mortality in a Cox proportional hazards model