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Generation of Normal Values for Respiratory Muscle Force Requires That the Control Group Be Examined Neurologically

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To the Editor:

We read with interest the article by Park et al.[1] on a cross-sectional study of 360 healthy controls to establish reference limits for respiratory muscle strength by measuring maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), and peak cough flow (PCF). To compare the strength of respiratory muscles with that of the limb muscles, a handgrip strength (HGS) test and five-time sit-to-stand test (FTSST) were also performed.[1] Respiratory muscle strength has been found to differ from values reported in studies from other countries and that MEP correlates with HGS.[1] It was concluded that reference limits for MEP, MIP, and PCF depend on the country and must be created separately for each nation.[1] The study is impressive, but several points require discussion.

The first limitation of the study is that it did not describe how healthy controls were assessed as healthy. In order to interpret the results, it is important to know how normality was defined. Of particular importance is how central nervous system (CNS) disorders, including spinal cord pathologies, that could affect respiratory muscle strength, were excluded. Were CNS disorders excluded based on medical history alone or did all included subjects systematically undergo clinical neurological examination, CNS imaging, or even cerebrospinal fluid (CSF) studies? The exclusion of CNS disorders is crucial as they can strongly influence MEP and MIP.

Since skeletal muscles are innervated by peripheral nerves, it is also important to exclude any peripheral nervous system (PNS) pathology that could have influenced the evaluated parameters. In particular, motor neuron disease, radiculitis, plexitis, and various neuropathies are known to have a strong influence on the muscle strength of the respiratory muscles. Involvement of the respiratory muscles is particularly known in amyotrophic lateral sclerosis, spinal muscular atrophy, Guillain-Barre syndrome, and various hereditary neuropathies.[2]

Since primary and secondary myopathies can affect the respiratory muscles,[3] it is also imperative to rule out these myopathies. In particular, myopathies involving the axial muscles and diaphragm must be off the table before these subjects are included in the study group.

Involvement of the respiratory muscles is also known in neuromuscular transmission disorders such as myasthenia gravis, myasthenic syndrome, or congenital myasthenic syndrome. We should therefore know whether each included patient actually underwent a neurological examination before inclusion in the study or not.

A second limitation is that it is not mentioned whether or not psychiatric illnesses were excluded as factors influencing the reference limits. Psychiatric disorders such as mood disorders, anxiety disorders, bipolar disorder, schizophrenia, dementia, or eating disorders are known to influence the performance of the respiratory muscles via central pathways.

MIP and MEP may also depend on the presence or absence of lung disease. Did all included patients undergo a comprehensive pulmonary examination before inclusion in the study? In this context, we should know how many “healthy” subjects were excluded due to abnormal lung function tests.

Another limitation is that comorbidities were not considered as factors influencing the reference limits of MIP and MEP. Especially in patients in the older age group, it is conceivable that they had age-related disease, such as orthopedic impairments, which could have had an influence on the results. In this context, we should know which medications the included patients regularly took and whether the patients were systematically screened for illegal drugs prior to inclusion. Particularly in younger age groups, it can be assumed that at least some of the patients included consumed illicit drugs regularly or irregularly.

A final limitation is that HGS and FTSST are weak parameters for assessing global muscle strength. HGS primarily tests the strength of the distal upper limb muscles, but not the axial muscles and diaphragm. FTSST mainly assesses the muscle strength of proximal lower limbs, but hardly assesses the strength of the distal lower limb muscles. It is not mentioned whether diaphragm function was tested in any of the included patients.

In summary, in order to generate reference limits for respiratory muscle strength, neurologically, psychologically, and orthopedically normal subjects must be selected.

Authors' Response to the Letter

We appreciate your interest in our study[1], and thank you for pointing out areas that the readers could consider. Many researchers are indeed grappling with how to define "normal," but the criteria are not yet clearly defined, which is an issue. While it's possible to identify individuals who are closer to the norm through extensive testing, doing so can lead to a substantial increase in both costs and time.

Respiratory muscle strength, as mentioned by you, is influenced by various factors, including central nervous system injuries, peripheral neuropathies, neuromuscular disorders such as muscular dystrophy, psychiatric illnesses, pulmonary diseases, and more. Therefore, recruiting participants who can be excluded from these conditions is a critical aspect.

While it could have been possible to define healthy controls by referring to another study[4-7] that screened individuals residing in the local community without any specific medical history, the authors aimed for a more precise definition of normal individuals. Therefore, we established reference values for MIP and MEP specific to different age groups from

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individuals who visited the Pusan National University Hospital Health Examination Center and had no abnormalities.

At the health examination center, physical exam (height, weight, blood pressure, pulse rate, abdominal circumference), blood test [Complete blood count, blood group test, metabolic function (glucose, lipid, electrolyte), organ function (liver, kidney, thyroid), vitamin D, uric acid, tumor markers, blood serum (rheumatoid factor, hepatitis A, B, C, and C-reactive protein test)], urinalysis, fecal test, ophthalmic exam, audiometry exam, cardiopulmonary exam (chest X-ray, pulmonary function test, electrocardiogram, chest CT), abdominal exam (abdominal ultrasound, gastroscopy), female exam (pelvic exam, cervical cytology, mammography), and arteriosclerosis exam were conducted. The sequence of the examination involved an initial assessment by a family medicine physician, followed by a health checkup, and ultimately, after reviewing the test results, the subjects were referred to the research team based on the findings of a specialist in family medicine.

In the case of central nervous system and peripheral nervous system disorders, a two-step exclusion process was employed during the subject recruitment process. This process involved an initial assessment by a family medicine physician and a confirmation of baseline health status by the research team. Specialized tests such as brain imaging and nerve conduction studies were not conducted. However, in conjunction with the assessment of respiratory muscle strength, we also conducted a HGS and the FTSST test to evaluate the functional status of the upper and lower limbs. As a result, we think it's highly unlikely to involve individuals with central nervous system injuries, peripheral nervous system abnormalities, or neuromuscular disorders.

For individuals with psychological disorders, the screening process at the health examination center involved initial assessments through psychological questionnaires, depression and anxiety scales, as well as surveys and confirmations regarding dementia. Additionally, individuals with respiratory diseases were explicitly excluded from the study, and comprehensive pulmonary examinations (including x-ray, and chest CT scans) were conducted. Finally, pulmonary function tests were performed, resulting in the exclusion of over 100 individuals.

We chose to utilize HGS[8] and FTSST as they are assessments easily measurable by anyone, anywhere. These tests are also prominent evaluation tools in geriatric assessments. Future research to confirm specific examinations, such as a diaphragm function test, may be necessary. However, there is uncertainty about whether the additional specific data obtained justifies the substantial extra cost investment.

The primary focus of this study is to establish Korean reference values for MIP and MEP based on individuals who have been assessed as healthy in routine general health check-ups. It is anticipated that the reference values for MIP, MEP will vary across different countries due to factors such as ethnicity, economic status, physical activity levels, and ongoing environmental changes. Therefore, periodic research on respiratory muscle strength in healthy controls from each country would be beneficial for setting exercise goals for patients. Once again, thank you for your interest in our study.

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