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Respiratory Muscle Performance Screening for Infectious Disease Management Following COVID-19: A Highly Pressurized Situation

Running Title: Respiratory Muscle Strength and Viral Infections

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Abstract

The 2019-2020 coronavirus pandemic elucidated how a single highly infectious virus can overburden healthcare systems of even highly economically developed nations. A leading contributor to these concerning outcomes is a lack of available intensive care unit (intensive care unit) beds and mechanical ventilation support. Poorer health is associated with a higher risk for severe respiratory complications from the coronavirus. We hypothesize that impaired respiratory muscle performance is an underappreciated factor contributing to poor outcomes unfolding during the coronavirus pandemic. While impaired respiratory muscle performance is considered to be rare, it is more frequently encountered in patients with poorer health, in particular obesity. However, measures of respiratory muscle performance are not routinely performed in clinical practice, including those with symptoms such as dyspnea. The purpose of this perspective paper is to discuss the potential role of respiratory muscle performance from the perspective of the coronavirus pandemic. We also provide a theoretical patient management model to screen for impaired respiratory muscle performance and intervene if identified with the goal of unburdening healthcare systems during future pandemic crises.

Clinical Significance

- Poor baseline health increases the risk of acute respiratory distress syndrome due to coronavirus infection and poorer outcomes.
- Patients with poorer baseline health, notably obesity, are more likely to demonstrate impaired respiratory muscle performance, and poorer outcomes following intensive care unit admission and mechanical ventilation.

- This relationship indicates respiratory muscle performance may contribute to outcomes related to acute respiratory distress syndrome from coronavirus infection in patients with poor baseline health.

Introduction

The 2019-2020 coronavirus (COVID-19) pandemic elucidated how a single highly infectious virus can overburden healthcare systems of even highly economically developed nations[1–5]. Of the serious complications that have arisen from this pandemic[3], the burden placed on intensive care units and mechanical ventilation due to acute respiratory distress syndrome is particularly concerning[1–5]. Some patients are unable to receive otherwise necessary and routine surgeries due to a lack of available intensive care unit and mechanical ventilation resources due to COVID-19[6]. This is notwithstanding the mortality rate of patients with acute respiratory distress syndrome due to COVID-19 who were able to receive intensive care unit care and mechanical ventilation support[2–5].

Even prior to the COVID-19 pandemic, intensive care unit and mechanical ventilation resources were heavily resourced[7]. Despite increases in total intensive care unit beds over the past decade, occupancy rates in the United States are approximately 66-68%[7] at any given time; some facilities reporting as high as 82.1%[7]. Currently, mechanical ventilation is used in approximately 33% of intensive care unit admissions[7] and is projected to increase 2.3%/year[8]. The number of patients requiring prolonged mechanical ventilation is also expected to increase, especially for older adults and patients with comorbidities[9]. There also appear to be surges in mechanical ventilation usage due to seasonal influenza[10]. Previous research indicates that United States could accommodate a surge of 26,200 to 56,300 cases requiring mechanical ventilation

with extensive pre-pandemic preparation[11]. With the surge in cases of acute respiratory distress syndrome due to the COVID-19 pandemic, vulnerabilities to the continuity of our healthcare system is apparent. Importantly, availability of these resources varies between states and geographical areas and, as such, some areas may be more heavily impacted than others.[12]

COVID-19 and other viral infections can cause significant damage to the lungs and airways potentially resulting in acute respiratory distress syndrome and, if severe enough, respiratory failure[13]. There are certain patient demographics that appear to be associated with a higher susceptibility to developing severe respiratory complications from COVID-19 requiring intensive care unit admission and mechanical ventilation[2–5,14]. These conditions included obesity, older age and smoking as well as cardiometabolic and lung disease[2–5]. Patients with these characteristics and pre-existing medical conditions are also at higher risk for serious complications from seasonal influenza[13,15,16]. Of note, obesity was present in nearly one third of hospitalizations and fatal cases during the 2009 H1N1 pandemic[13]. However, not all patients sharing these characteristics experience similar outcomes during this pandemic or even became infected. There are also people who do not possess these characteristic who require mechanical ventilation and intensive care unit admissions due to the COVID-19 pandemic[17–23]. As such, there are other, underappreciated factors contributing to the risk for poor outcomes resulting from the COVID-19 pandemic observed in admitted patients beyond the aforementioned risk factors.

We hypothesize that the outcomes associated with these demographics is impaired respiratory muscle performance. While impaired respiratory muscle performance is considered to be rare[24,25], it is more frequently encountered in patients possessing poor health characteristics, in particular obesity. Measures of respiratory muscle performance are also not routinely performed

in clinical practice, even in patients presenting with dyspnea[26–28]. The purpose of this perspective paper is to discuss the potential role of respiratory muscle performance regarding the COVID-19 pandemic. We also provide a theoretical model to screen for impaired respiratory muscle performance and intervene when identified with the goal of unburdening the healthcare system during future pandemic crises.

Respiratory Muscle Physiology and Pathophysiology

In healthy individuals with normal total respiratory system compliance, the opening pressure required to fully inflate the alveoli is approximately 40cmH2O[29–33]. The ability to recruit the lungs is necessary for pulmonary hygiene behaviors such as yawning and coughing[34]. Tidal breathing in healthy individuals only requires ≈5-10cmH_2O[29–33]. The average maximal inspiratory pressure generated by a healthy adult aged 18-29 years is 128cmH_2O (116.3-139.5cmH_2O) for males and 97cmH_2O (88.6-105.4cmH2O) for females. By comparison, the average maximal inspiratory pressure for a healthy adult aged 70-83 years is 76.2cmH_2O (66.1-86.4cmH_2O) for males and 65.3cmH_2O (57.8-72.7cmH_2O) for females[24]. In healthy adults, the pressure needed for both full breaths and quiet breathing represents a small fraction of the respiratory muscles maximal pressure generating capacity[24] (**Table 1**). The disparity between the pressure demands of breathing and peak pressure generating capacity of the respiratory musculature allows spontaneous breathing to occur with high efficiency (i.e., low energy costs and a large reserve).

Several factors decrease respiratory muscle performance (e.g., aging, obesity, physical inactivity, smoking, and chronic disease)[35–38] . In patients with obesity and chronic lung diseases, in addition to a reduction in respiratory muscle strength, the demand imposed on the respiratory muscle also increases due to changes in airway resistance and chest wall mechanics[35–37]. Quiet

breathing accounts for 1-3% of total oxygen consumption in normal weight, healthy individuals [35,39]. In obese individuals, the demand imposed on the respiratory muscle increases more than three-fold[39], increasing total respiratory muscle oxygen consumption to more than 14%[35,39]. In an acutely diseased lung (e.g., acute respiratory distress syndrome), the pressure required to breathe further increases[40]. Therefore, obese patients sustaining an acute viral infection can experience further imbalances between respiratory muscle force generating capacity and imposed demands required for breathing, increasing the risk for respiratory failure[40].

In patients with severe acute respiratory distress syndrome and respiratory failure, mechanical ventilation may be required to offload the respiratory musculature. However, mechanical ventilation has been shown to induce rapid atrophy and profound weakness of the respiratory musculature[41–43]. Adverse changes in the respiratory muscles due to mechanical ventilation have been defined as Ventilator Induced Diaphragm Dysfunction (VIDD) and may occur after only 18hrs of mechanical ventilation[41–43]. These effects of VIDD makes it difficult for patients to successfully wean from mechanical ventilation by creating an imbalance between respiratory muscle force generating capabilities and the demand imposed for spontaneous breathing[19,21,22,44,45]. Lower diaphragm thickness even at the outset of mechanical ventilation is associated with delayed weaning from mechanical ventilation and a higher risk of complications[46]. Unsuccessful weaning from mechanical ventilation due to VIDD may be exacerbated in patients with baseline respiratory muscle performance impairments as many are also risk factors for failing to wean[17,18,20,22,23]. This relationship is especially concerning in obese patients[17,18,20]. Obesity has been shown to increase the length of stay and need for mechanical ventilation even due to influenza infection[16], and results in poorer outcomes[15].

Current Respiratory Muscle Testing in Clinical Practice

Effective preventive strategies are contingent upon the use of valid and reliable screening tools and assessments in patients with higher pretest probability[40]. It is generally not recommended that all patients receive the same screening tests in order to minimize costly false positives[40]. Respiratory system screening tools are recommended for patients with symptoms consistent with respiratory muscle impairment, most notably dyspnea[26–28].

In patients with dyspnea, the *US Preventive Services Task Force* and Joint Guidelines of the *American College of Physicians*, *American College of Chest Physicians*, *American Thoracic Society (ATS)*, and the *European Respiratory Society (ERS)* recommend the use of spirometry and other examinations for screening and eventual diagnosis[26–28]. However, these guidelines and statements do not include assessment of the respiratory musculature[26–28]. Even in the Practice Advisory for Pre-anesthesia Evaluation by the *American Society of Anesthesiologists*, respiratory muscle assessment is not included in routine preoperative assessment, even for higher risk patient populations[47].

The omission of respiratory muscle performance testing in guidelines for dyspnea assessment and respiratory disease screening is surprising. The ATS and ERS have produced guidelines on respiratory muscle testing procedures[36,37] and normative values for respiratory muscle performance exist[24,25]. Moreover, criteria/thresholds for defining respiratory muscle weakness have been proposed [24,25,36,37].

Available evidence does indicate that respiratory muscle weakness is rare in the general population[24,25]. The threshold for respiratory muscle weakness in a younger healthy adult is also fairly low (i.e., >40years of age: 63cmH_2O)[25]. However, respiratory muscle weakness is associated with dyspnea[28], and there are certain populations where respiratory muscle weakness is more likely[17,48,49]. Even in healthy older individuals, the maximal inspiratory pressure

produced by the respiratory musculature decreases[24]. However, due to the normal age-related changes in lung compliance and muscle strength the threshold for respiratory muscle weakness with aging is also lower (i.e., >80 years: 42cmH_2O)[25]. It is important to acknowledge that these age-related reductions are in reference to healthy individuals. As described earlier, in patients with multimorbidity, the risk of respiratory muscle weakness may increase or potentially compound these age related reductions in respiratory muscle performance[35,38]. While routinely screened measures of lung volume and flow rate are associated with respiratory muscle performance[36,37], changes in respiratory muscle performance may occur independently of these values and may be detected prior to changes in lung volume[36,37,49,50].

Respiratory Muscle Performance Testing

The use of non-invasive handheld manometers to assess Maximal Static Inspiratory Pressure quantifies respiratory muscle strength across multiple populations with varying characteristics[36,37,51] with excellent reliability[52]. The ATS and ERS have provided standardized protocols testing when using handheld devices[36,37] which are affordable and easily accessible.

To assess maximal inspiratory pressure, individuals are instructed to fully expire and then perform a maximal inspiratory effort for at least 1.5 seconds[36,37]. The peak negative pressure sustained for at least 1 second during that inspiratory maneuver is considered the maximal inspiratory pressure[36,37]. A minimum of three trials are performed with 1 minute of rest between trials and the highest value recorded defining maximal inspiratory pressure[36,37]. Acceptable values for each trial should be within 10% of each other.

Another test to assess respiratory muscle performance is the Test of Incremental Respiratory Endurance (TIRE)[53]. The TIRE requires the patient to breathe in through the manometer from residual volume to total lung capacity and to sustain that breath for as long as

possible[53]. Due to the nature of this test the TIRE provides maximal inspiratory pressure and several other measurements of respiratory muscle performance. Inspiratory duration, which is measured in seconds, represents the duration of maximal sustained inhalation (i.e., endurance)[53]. Sustained Maximal Inspiratory Pressure is expressed in Pressure Time Units or Joules and represents single breath work capacity[53]. Both the Sustained Maximal Inspiratory Pressure and the slope of its curve are emerging clinical measures across several populations[54,55]. The combination of these values provide a more comprehensive assessment which may identify characteristics of respiratory muscle weakness or fatiguability that may be missed when only measuring maximal inspiratory pressure[55]. An example of this is demonstrated in **Figure 1**; an individual with a higher maximal inspiratory pressure may conversely demonstrate a much lower capacity for producing work over time. At this time, there is only a single study that has proposed normative values for TIRE[56]. In addition, reliability and validity for the TIRE has only been reported in patients with chronic obstructive pulmonary disease[54]. Additional research is needed to further assess the validity and reliability of the TIRE, as well as further establish normative values for comparison in patient populations.

Respiratory Muscle Training

Respiratory muscle training improves respiratory muscle strength, exercise capacity, diaphragm muscle thickness, and dyspnea in several patient populations[57–61]. Patients exhibiting the most profound baseline respiratory muscle weakness tend to receive the greatest benefit from respiratory muscle training. Those in poor health and at risk for viral infection (e.g., influenza) may demonstrate respiratory muscle weakness and thus be at increased risk of a poorer clinical trajectory if acute respiratory distress syndrome ensues. However, even in healthy individuals without dyspnea, respiratory muscle training has also been shown to

provide modest benefits on exercise performance[62]. Conventional respiratory muscle training protocols require breathing through a device with valve set to a pressure threshold. Once enough pressure is generated, the valve opens and air flows through the device. A percentage of the maximal inspiratory pressure is used as the training load based on the type of protocol. Training protocols typically use resistive loads ranging between 30-80% of maximal inspiratory pressure. One of the unique advantages of respiratory muscle training is that it can be implemented in shorter intervals (30 breaths, 2 times/day). Training effects from respiratory muscle training have been observed for multiple protocols lasting only 4 weeks[60,63,64]. For patients with dyspnea and/or sedentary, these training characteristics may promote adherence and compliance to training[65,66].

Currently, no studies have directly investigated the role of respiratory muscle training to reduce the risk of respiratory failure due to viral infection. Pre-operative respiratory muscle training has been shown to reduce the risk of post-operative respiratory complications[67–70]. Mans et al demonstrated that preoperative respiratory muscle training may reduce the risk of post-operative pulmonary complications following cardiothoracic or abdominal surgery by half[70]. A recent study by Chen et al found that a 5-day intensive pre-operative respiratory muscle training protocol resulted in significant reductions in both pulmonary complications and length of hospitalization[71]. Four weeks of respiratory muscle training at 50% of maximal inspiratory pressure has been shown to reduce hospital length of stay, mortality and the risk of intubation in patients at risk for prolonged hospitalization[72]. In patients requiring mechanical ventilation, respiratory muscle training improves weaning outcomes[73] and reduce hospital length of stay[74]. Evidence regarding the beneficial effects of respiratory muscle training is strong and the connection between impaired respiratory muscle performance, mechanical ventilation and

respiratory complications is also apparent. While the role of respiratory muscle training to mitigate the respiratory complications of viral infection in susceptible patients has yet to be investigated, currently available evidence supports further exploration of respiratory muscle training to reduce the risk of severe complications during a viral infection.

Theoretical Risk Reduction Model

A model to improve outcomes and reduce the burden of future viral pandemics may involve respiratory muscle performance screening. This model and its potential downstream effects on available mechanical ventilation and intensive care unit resources are illustrated in **Figure 2**. Patients with increased risk for acute respiratory distress syndrome and respiratory failure due to viral infection would receive this screening. If impaired performance is identified, patients could then be prescribed a respiratory muscle training program to implement at home. Patients would receive follow up after 4 weeks of training to assess progress. A telehealth or mobile app-based model would allow for the opportunity for real-time remote monitoring of compliance and assessment. Telehealth and home-based models for respiratory muscle training have been studied with similar effects[75–77].

The timing of this initial screening could occur during routine annual follow up. Another approach could be to implement this screening when at-risk patients receive vaccinations prior to flu season with hopes of "inoculating" patients from severe respiratory complications due to viral infection, at the same clinical "touchpoint" for seasonal vaccinations. With rapidly advancing mobile technology, at-risk patients who have already received their device could even perform their own monitoring at home. Long term participation in respiratory muscle training may be necessary for maintenance of improvements following training. Even with 12 weeks of respiratory muscle training, the effects gradually decline after 1 year if patients do not

performance maintenance respiratory muscle training[78] or participate in vigorous aerobic exercise[79,80]. However, since the effects of respiratory muscle training have been shown to occur even within 5 days of training[71], at the first outbreak of a viral pandemic, at-risk patients could be advised to initiate an urgent prophylactic respiratory muscle training protocol. Initiating respiratory muscle training following intensive care unit admission requiring mechanical ventilation support due to acute respiratory distress syndrome could also help accelerate recovery and discharge home.

This model could potentially result in substantial downstream benefits by reducing the number of infectious cases requiring intensive care unit and mechanical ventilation during a pandemic. This would also make intensive care unit and mechanical ventilation resources more available for non-pandemic related care.

Conclusion

In times of crisis, it is important to remember our experiences and lessons learned from COVID-19; from a healthcare perspective a primary lesson is we need to be better prepared moving forward. This preparation for the future entails exploring and testing plausible solutions that have not been considered. As described in this concept paper, it appears diminished respiratory muscle performance, in conjunction with other disconcerting characteristics (e.g., obesity, chronic diseases), may contribute to the overwhelming burden imposed on healthcare systems due to viral pandemics. What is more concerning is that frequency of viral pandemics, and the prevalence of the global population at poor health associated with impaired respiratory muscle performance are potentially both at the tipping point. In nations with high economic development, poor baseline health is now, unfortunately, the norm; obesity alone is present in now 42.4% of the adult population in the United States and continues to increase[81]. Another

troubling trend is the presence of multimorbidity in older adults[82], a population that also continues to increase[83].

Given how these issues intersect in a multitude of ways, we propose that screening for respiratory muscle impairment in patients with dyspnea or characteristics associated increased risk of severe respiratory complication due to viral infection may be advantageous. Furthermore, in patients identified as having respiratory muscle impairments, respiratory muscle training may prove valuable in mitigating the health impact of future pandemics.

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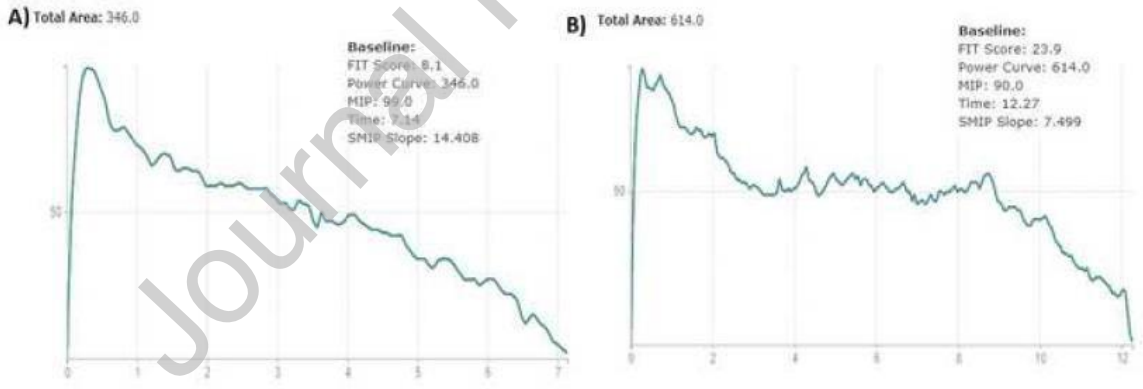

Figure 1. Comparison of patients with same maximal inspiratory pressure **but vastly different performance in other characteristics of respiratory muscle performance**

This image represents the results the TIRE performed on two separate obese patients. The maximal inspiratory pressure in patient A is higher (A: 99cmH_2O vs B: 90cmH_2O) but when

plotted over time the peak work capacity is much lower than patient B (A: 346 PTU vs, B: 614 PTU). This demonstrates the additional information regarding respiratory muscle performance that can be gleaned from the TIRE compared to assessing maximal inspiratory pressure alone.

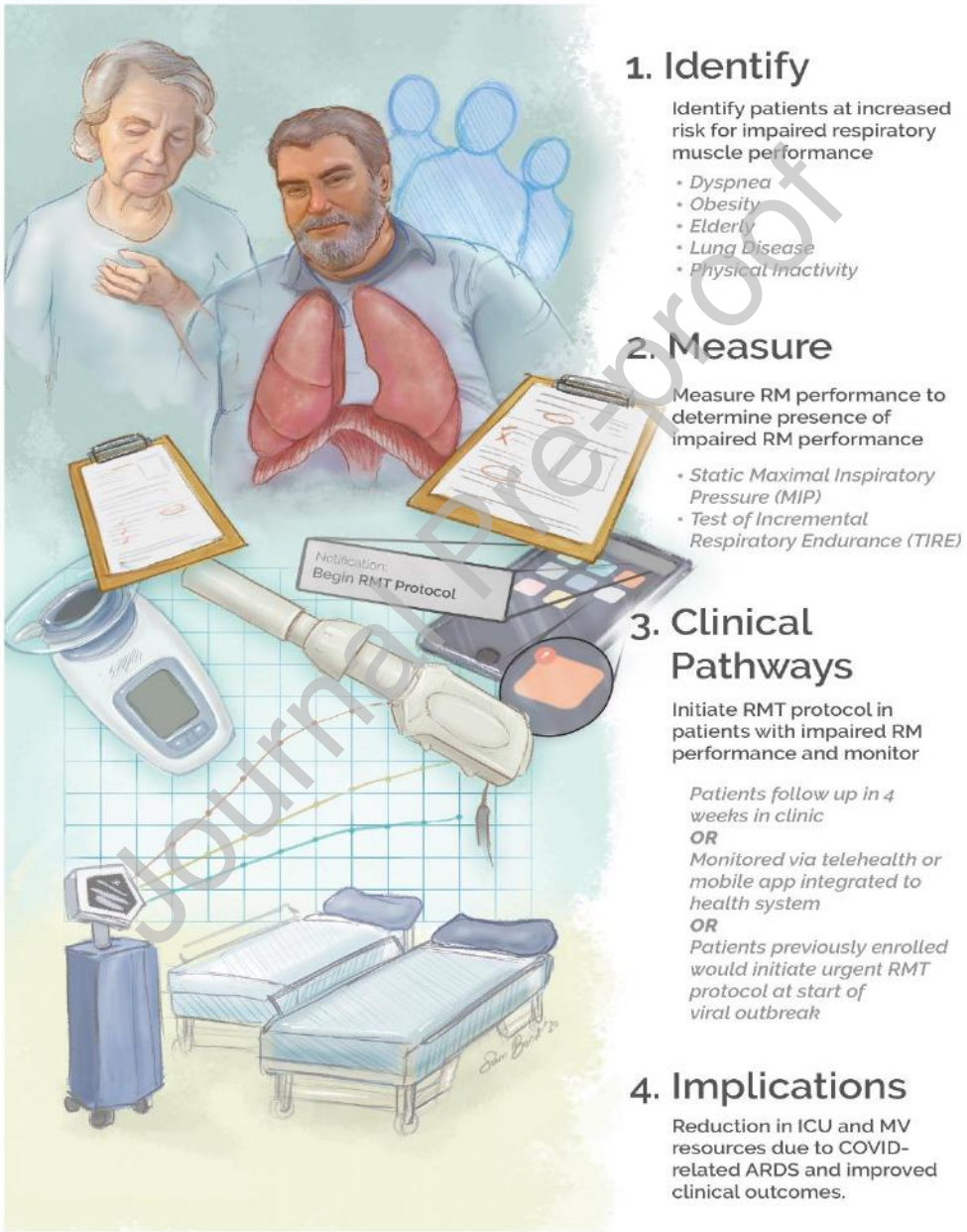

Figure 2. Theoretical Risk Reduction Model

This model describes our theoretical patient management model which includes 4 components: 1) Identify patients at increased risk for impaired respiratory muscle (respiratory muscle) performance. 2) Measure respiratory muscle performance in patients screened for high risk of impaired respiratory muscle performance using either static maximal inspiratory pressure or the Test of Incremental Respiratory Endurance. 3) Clinical pathways for respiratory muscle training (respiratory muscle training) in patients with impaired respiratory muscle performance, which involve either: follow ups every 4 weeks in clinic OR home based monitoring using telehealth or mobile apps OR patients previously enrolled would initiate an urgent 5 weeks protocol at the start of an outbreak by receiving a notification on their mobile app. 4) The downstream benefits would involve reducing the utilization of intensive care unit and mechanical ventilation resources due to COVID related acute respiratory distress syndrome, and improving clinical outcomes.