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Case Report

A 64-year-Old patient assigned male at birth with COPD and worsening dyspnea while on estrogen and antiandrogen agents

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ABSTRACT

Among patients with COPD, ventilatory inefficiency in response to exercise can be due to respiratory muscle dysfunction or expiratory flow limitation causing air-trapping and dynamic hyperinflation. We discuss a case of severe ventilatory limitation in response to exercise due to reduced respiratory muscle mass in the setting of gender-affirming hormone therapy (GAHT), and how the interpretation of pulmonary function testing (PFT) and respiratory symptoms among transgender and gender diverse (TGD) patients can be influenced by GAHT.

1. Introduction

The percentage of adults in The United States who self-identify as lesbian, gay, bisexual, transgender or something other than heterosexual has increased to a new high of 7.1%, which is double the percentage from 2012 [1]. This emphasizes the need for further education directed at Pulmonary, Critical Care, and Sleep Medicine physicians on the general concepts of gender-affirming care, as well as the clinical nuances of gender-affirming hormone therapy (GAHT), which could significantly improve patient-provider interactions and humanize care. As clinicians, we need to better understand and honor the unique needs of different members of the Lesbian, Gay, Bisexual, Transgender, Queer and Intersex (LGBTQI+) community. In this article, we discuss the effect of GAHT on respiratory physiology, and how not accounting for changes in body composition as a result of GAHT may results in gender disparity issues potentially present in almost every scenario where PFT are needed to guide diagnosis, decision making and treatment allocation.

2. Case presentation

A 64-year-old patient, assigned male at birth, presented for candidacy assessment of lung volume reduction surgery (LVRS) in the setting of chronic obstructive pulmonary disease (COPD) and worsening dyspnea during exertion approximately over the last three

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years. New York Heart Association heart failure classification was class III with a Karnofsky score of 70%. Aside from dyspnea, there were no accompanying changes in COPD exacerbation frequency, cough or sputum production, or chest pain. Patient had started gender-affirming hormone therapy (GAHT) for gender incongruence approximately three years prior to this evaluation. Patient's current GAHT included *estradiol* 10 mg *intramuscularly every 7 days, spironolactone* 50 mg *orally twice a day, and finasteride* 5mg *orally every day*. Patient's past medical history includes tobacco use (45 pack year, quitting almost 2 years prior), COPD (GOLD 3B classification) on oxygen supplementation per nasal canula at rest (2 L/min) and during exertion (3L/min) on appropriate inhalation therapy with fluticasone, umeclidinium, and vilanterol. Prior to consultation, the patient had been deemed not a candidate for endobronchial valve lung volume reduction (EVLVR), LVRS, or lung transplantation by an outside institution.

2.1. Physical examination findings

During the initial outpatient visit, the patient's vital signs were normal with oxygen saturation of 92% on 2 L/min of oxygen per nasal cannula. The patient's weight was 83.6 kg and represented a 13.7 kg weight gain over the last three years, with a body mass index (BMI) of 28 kg/m^2 (compared to 21 kg/m^2 three years ago). The patient was alert, oriented and not in acute distress. The examination of head, eyes, ears, nose, and throat; chest; heart; and extremities revealed the following: normocephalic and atraumatic, normal conjunctiva, regular heart sounds and rhythm, reduced breath sounds without wheezing, rhonchi, or rales. The remainder of the physical examination was normal.

2.2. Diagnostic studies

The patient's laboratory results indicated a hemoglobin level of 14.4 g/dL, WBC count was 11,360/μL, and platelets were 323,000/μL. The sodium level was 140 mM, potassium level was 4.7 mM, bicarbonate level was 23 mM, BUN level was 21 mg/dL, and creatinine level was 0.82 mg/dL. The liver function tests were normal. The alpha-1-antitrypsin level was 165 mg/dL. The patient's myoglobin was normal at 48 ng/mL, while the troponin was slightly elevated at 0.67 ng/mL. The patient's ECG showed a normal sinus rhythm with a normal axis, low voltage QRS and no signs of acute ischemia.

The pulmonary function testing (PFT) showed moderate obstruction with a forced expiratory volume in the first second (FEV1) to forced vital capacity (FVC) ratio of 45% predicted, FEV1 of 1.59 L (49% predicted) with acute bronchodilator response, and severe reduction in diffusing capacity (26% predicted). Lung volumes were normal with a total lung capacity (TLC) of 7.25L (106% predicted). The computed tomography of the chest without intravenous contrast showed advanced centrilobular emphysema primarily in the upper lungs with associated bullae, paraseptal emphysema in the lower lobes, mild scarring at the lung bases, tiny pulmonary nodules, wasting of the chest wall inner and outer musculature, and the presence of breast tissue. The ventilation perfusion study with quantification showed relatively homogeneous perfusion throughout the lungs, best maintained to the mid and lower lungs, without segmental wedge-shaped defects or convincing mismatched defects. There was no evidence of right heart failure or elevated pulmonary vascular pressures on echocardiogram. Overall, there was no significant change in spirometry parameters or radiographic appearance of underlying emphysema over the last three years. The patient's exercise capacity was assessed utilizing the National Emphysema Treatment Trial (NETT) protocol, the patient exercised for 12.9 minutes to a very low maximum exercise level of 55 W (35% predicted) with moderately reduced oxygen consumption at 57% predicted. A significant ventilatory limitation by maximal voluntary ventilation (MVV) criteria was noted, with a breathing reserve of 4%.

3. Discussion

What is the diagnosis? COPD, GOLD 3B classification with *severe ventilatory limitation* in response to exercise due to *reduced respiratory muscle mass* in the setting of GAHT.

The breathing reserve (BR) is expressed as either the difference between the maximal voluntary ventilation (MVV) and the maximum exercise ventilation (VE) in absolute terms, or this difference as a fraction of the MVV [2,3]. The resting ventilatory reserve indicates the potential for increasing ventilation rate, and therefore the potential for increasing the intensity of physical activity [3]. Among patients with COPD, ventilatory inefficiency in response to exercise can be due to respiratory muscle dysfunction or expiratory flow limitation causing air-trapping and dynamic hyperinflation [4]. However, in this case, there was no evidence of either worsening parenchymal changes, or longitudinal progression of baseline expiratory flow limitation that correlated with the patient's symptoms. Despite advanced centrilobular emphysema and radiographic evidence of hyperinflation, PFT *did not* reflect the presence of hyperinflation (TLC of 7.25L, 106% predicted). However, significant wasting of chest wall inner and outer musculature was noted (Fig. 1).

While the terms “transgender” and “gender diverse” are used for individuals whose gender identity differs from the stereotypic gender constructs associated with their respective sex assigned at birth, our patient did not identify with these specific terms [1]. Nonetheless, the patient was on estrogen and antiandrogen agents used in GAHT regimens for the management of people experiencing gender incongruence [5]. How does GAHT influence the interpretation of PFT and respiratory symptoms among transgender and gender diverse (TGD) patients? Considering the evolution of gender-affirming care, there is increasing uncertainty in the medical community on whether gender or sex should be used to calculate predicted normative values for PFT in TGD patients. The changes in body composition as a result of GAHT, such as muscle strength and hemoglobin levels, could potentially influence the results and interpretation of PFT based on sex [6,7]. For example, GAHT that is estrogen-based can decrease muscular strength, lean body mass and muscle area, all of which could affect forced inspiratory lung volume, expiratory flow rate and resting lung volume [7]. Available data suggest that the maximum effect on muscle physiology will occur within one to two years of GAHT [6,7]. When in this case the normative values for the population assigned female-at-birth rather than male-at-birth are used to interpret the PFT results, hyperinfla-

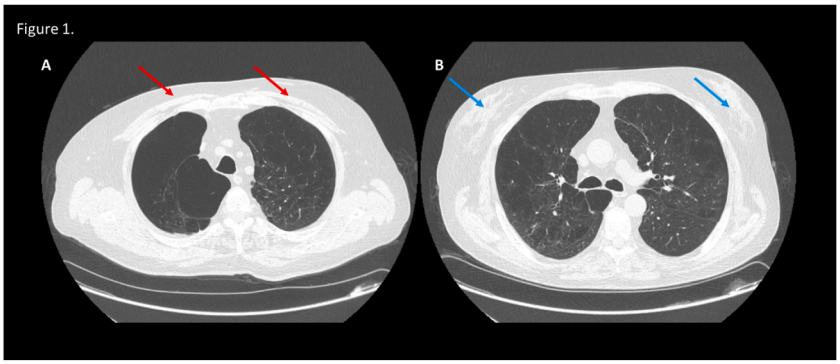

Fig. 1. Computed tomography of the chest without intravenous contrast
Images shows advanced centrilobular emphysema greatest in the upper lungs with associated bullae, tiny pulmonary nodules, wasting of chest wall musculature (A, *red arrow*), and the presence of breast tissue (B, *blue arrow*). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

tion becomes apparent (TLC 123% predicted) (Table 1B), and it more accurately reflects the patient's pulmonary symptoms and radiographic findings.

Although the American Thoracic Society (ATS) guidelines recommend using sex designated at birth as reference for normative values when interpreting PFT [8], using sex (instead of gender identity) to calculate predicted spirometry values when GAHT is established (1–2 years) could have a significant impact on test interpretation, and place TGD patients at risk for misdiagnosis and inappropriate treatment. Issues with representation in clinical prediction models and healthcare algorithms are largely unrecognized for sex and gender. Among TGD patients, changes in body composition as a result of GAHT could generate gender disparity issues when PFT are used to guide diagnosis, decision making and treatment allocation. [1]. In addition to understanding the extent and impact of GAHT on lung function, identifying appropriate normative values for PFT interpretation could also help in guiding adjustments in long-term GAHT based on changes in lung function, further improving the care of TGD patients.

Although this patient did not qualify for EVLVR based on established criteria (residual volume ≥175% predicted and FEV1 between 15 and 45% predicted) [9], the detection of hyperinflation when PFT were analyzed using normative values for individuals assigned female at birth, rather assigned male at birth (Table 1), could have had a significant impact in other clinical circumstances. Treatment allocation scenarios potentially affected by the sex based PFT interpretation in TGD patients may include preoperative physiologic pulmonary evaluation for lung resection, where predicted postoperative values for FEV1 and DLCO are estimated [10].

Additionally, the potential impact of GAHT on pulmonary mechanics mediated by body composition changes (such as muscular strength, lean body mass and muscle area) [7] makes regular monitoring of muscle strength and pulmonary symptoms important aspects of effective delivery of care among TGD patients with chronic pulmonary diseases and air-flow limitation. BMI-normalized handgrip strength and maximal respiratory pressures can be used as longitudinal monitoring tools of the effects of GAHT on muscular strength [11]. Results of this clinical monitoring could guide adjustments in long-term GAHT based on changes in lung function, in order to further improve the care of patients who are TGD.

Clinical Course. In the absence of other modifiable factors contributing to patient's dyspnea, and reconciling patient's GAHT needs with the potential benefits of lung volume reduction in the setting of advanced COPD, patient was deemed a candidate for LVRS [12,13] via bilateral thoracoscopic approach. Surgical procedure will be performed following further pulmonary rehabilitation and workup as indicated by the NETT protocol [12].

4. Conclusion

This case highlights the importance of appropriately understanding the changes in pulmonary function that occur as gender-affirming therapies are established, and the need for establishing a personalized approach to PFT interpretation in TGD patients. Further research in this area could inform both clinicians and TGD patients during their gender-affirming journey, offering very important tools to aid shared-decision making, pulmonary health monitoring and patient-centered healthcare for the TGD population.

Key learning points

- **Regular monitoring of muscle strength and pulmonary symptoms are important aspects of effective delivery of care for TGD patients with chronic pulmonary disease who are receiving GAHT.**
- **When approaching clinical scenarios where there is a discrepancy between clinical presentation and tests results, clinicians may be better equiped by assessing both sets of normative predictive values (female-, and male-assigned at birth) when interpreting PFT in TGD patients receiving GAHT.**
- **Issues with representation in clinical prediction models and healthcare algorithms are largely unrecognized for sex and gender. Establishing a personalized approach to PFT interpretation in TGD patients could mitigate gender disparity issues when PFT are used to guide diagnosis, decision making and treatment allocation in this patient population.**

Table 1
Pulmonary function testing.
Patient's pulmonary function results are compared to normative values for the population assigned male-at-birth (Table 1A) and the population assigned female-at-birth (Table 1B). Lower limit of normal (LLN), percentage of predicted (%pred), post-bronchodilator (PB), total lung capacity (TLC), functional residual capacity measured by plethysmography (FRCpleth), residual volume (RV), ratio of RV to TLC (RV%TLC), largest measured vital capacity (VC MAX), forced expiratory volume in the first second (FEV1) to forced vital capacity (FVC) ratio (FEV1/FVC), single-breath diffusing capacity of the lung (DLCO_SB), single-breath alveolar volume (VA_SB). Lung volumes and spirometry parameters are expressed in liters (L), and diffusion capacity is expressed as mL/(min*mmHg).

A. Normative values: Male-assigned at birth

LUNG VOLUMES			Normal		LLN	Found	%Pred
TLC			6.87		5.48	7.25	106%
FRCpleth			3.53		2.45	4.52	128%
RV			2.24		3.28	2.52	112%
RV%TLC			32		43	35	108%
Spirometry	Normal	LLN	Found	%Pred	PB-Found	%Change	PB-%Pred
VC MAX	4.27	3.22	4.70	110%	4.92	5%	115%
FVC	4.27	3.22	4.60	108%	4.79	4%	112%
FEV1	3.28	2.43	1.59	49%	1.79	12%	54%
FEV1/FVC	77.1	64.5	34.6	45%	37.3	8%	48%
DIFUSSION CAPACITY				Normal	LLN	Found	%Pred
DLCO_SB				25.8	19.2	6.6	26%
VA_SB				6.17	4.96	6.21	101%

B. Normative values: Female-assigned at birth

LUNG VOLUMES			Normal		LLN	Found	%Pred
TLC			5.91		4.74	7.25	123%
FRCpleth			3.28		2.34	4.52	138%
RV			2.13		3.22	2.52	118%
RV%TLC			36		48	35	98%
Spirometry	Normal	LLN	Found	%Pred	PB-Found	%Change	PB-%Pred
VC MAX	3.56	2.65	4.70	132%	4.92	5%	138%
FVC	3.56	2.65	4.60	130%	4.79	4%	135%
FEV1	2.76	2.05	1.59	58%	1.79	12%	65%
FEV1/FVC	78.3	65.8	34.6	44%	37.3	8%	48%
DIFUSSION CAPACITY				Normal	LLN	Found	%Pred
DLCO_SB				21.7	16.2	6.6	30%
VA_SB				5.73	4.59	6.21	108%

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Contributions

Cortes-Puentes GA drafted the initial manuscript, Davidge-Pitts CJ and Gonzalez CA provided important insight on transgender health, Cortes-Puentes GA, Dulohery-Scrodin, MM, Kennedy CC, and Lim KG all provided important content expertise on COPD and PFT data. All authors substantially revised and edited the final version of the manuscript.

Declaration of competing interest

The authors listed above report that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

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