CASE REPORT

Cardiopulmonary Exercise Test in the Detection of Unexplained Post-COVID-19 Dyspnea

A Case Report

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Summary

There is emerging evidence of prolonged recovery in survivors of coronavirus disease 2019 (COVID-19), even in those with mild COVID-19. In this paper, we report a case of a 39-year-old male with excessive body weight and a history of borderline values of arterial hypertension without therapy, who was mainly complaining of progressive dyspnea after being diagnosed with mild COVID-19. According to the recent guidelines on the holistic assessment and management of patients who had COVID-19, all preferred diagnostic procedures, including multidetector computed tomography (CT), CT pulmonary angiogram, and echocardiography, should be conducted. However, in our patient, no underlying cardiopulmonary disorder has been established. Therefore, considering all additional symptoms our patient had beyond dyspnea, our initial differential diagnosis included anxiety-related dysfunctional breathing. However, psychiatric evaluation revealed that our patient had only a mild anxiety level, which was unlikely to provoke somatic complaints. We decided to perform further investigations considering that cardiopulmonary exercise test (CPET) represents a reliable diagnostic tool for patients with unexplained dyspnea. Finally, the CPET elucidated the diastolic dysfunction of the left ventricle, which was the most probable cause of progressive dyspnea in our patient. We suggested that, based on uncontrolled cardiovascular risk factors our patient had, COVID-19 triggered a subclinical form of heart failure (HF) with preserved ejection fraction (HFpEF) to become clinically manifest. Recently, the new onset, exacerbation, or transition from subclinical to clinical HFpEF has been associated with COVID-19. Therefore, in addition to the present literature, our case should warn physicians on HFpEF among survivors of COVID-19.

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Key words: SARS-CoV-2, Dysfunctional breathing, Anxiety, Heart failure

Since the outbreak of coronavirus disease 2019 (COVID-19) in Wuhan, Hubei Province, China, in 2019, the rapid spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has taken tremendous proportions.[1)] Except for acute COVID-19, the condition with prolonged COVID-19-related symptomatology has also been recognized and recently nominated as post-acute COVID-19 or chronic COVID-19 with regard to symptom duration (beyond 3 or 12 weeks after symptom onset).[2)] Although the exact reason for prolonged recovery in some patients with COVID-19 is not yet determined, a possible explanation could be hidden in the joint action of reinfection, immunological and inflammatory factors, and weak or absent antibody response, as well as psychological issues.[2)] According to investigations from one prospective cohort, the most common symptoms during COVID-19 follow-up were breathlessness, fatigue, and insomnia (39%, 39%, and 24%, respectively).[3)] Although only minority of those patients had abnormal chest X-ray or restrictive lung function on spirometry testing (14% and 11%, respectively) during follow-up, nearly 60% of patient with mild COVID-19 experienced prolonged symptoms.[3)] Those findings indicate a possible development of long-term COVID-19 complications, regardless of prior COVID-19 severity. Considering the complexity of post-COVID-19 syndromes, the great need for its holistic assessment and management is entirely understandable, as suggested in recent guidelines.[4)] However, physicians may face a more complicated scenario when prolonged COVID-19 symptoms in some patients are not comparable

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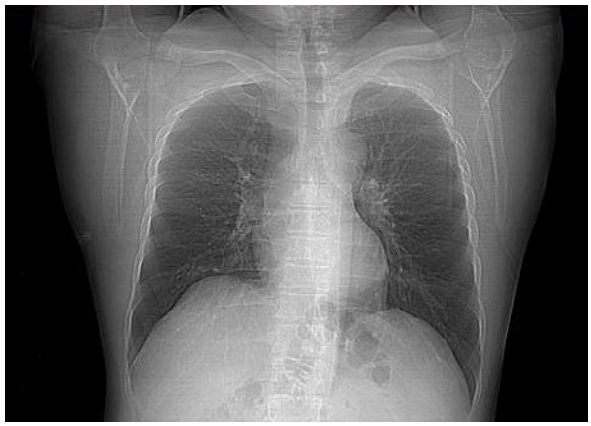

Figure 1. Normal posteroanterior chest X-ray.

with cardiopulmonary diagnostic findings. In this sense, we report a case of a male patient who had prolonged dyspnea after mild SARS-CoV-2 infection, without initial confirmation of any underlying cardiopulmonary disorder.

Case Report

A 39-year-old male was admitted with a history of fever of up to 38.4°C that lasted for 3 days, dry cough, and fatigue. He reported measuring increased blood pressure (BP) values (up to 145/90 mmHg) periodically in the past few years, but he did not use antihypertensive therapy. Otherwise, no other underlying diseases, bad habits, or allergies have been reported. His physical and cardiovascular examination was normal, except he was overweight (body mass index (BMI), 29.4 kg/m^2) and was subfebrile (37.3°C). Initial laboratory revealed decreased lymphocyte count (12%; reference range, 20%-46%) and increased C-reactive protein (CRP, 13 mg/L; reference range, < 5 mg/L), whereas other laboratory findings were in the reference range. Chest X-ray was normal, whereas real-time polymerase chain reaction assay was positive for SARS-CoV-2 infection. After being diagnosed mild COVID-19, vitamins and antipyretics were prescribed, and he was referred to home isolation. Two weeks after, he was feeling well and symptom-free.

Two months after the mild COVID-19, the patient referred to a pulmonologist in the outpatient clinic, complaining about recurrent breathlessness during physical exertion, periodical fatigue, deep sighing, light headache, and neck and shoulder muscle stiffness, which presented for more than a month, with significant worsening in the past seven days. He denied having current complaints before SARS-CoV-2 infection. The physical examination and vital signs were normal, and all laboratory results were in normal range, including complete blood count (leukocytes, 7.4 × 10^9/L; lymphocytes, 32%; hemoglobin, 142 g/L; thrombocytes, 226 × 10^9/L), markers of coagulation (D-dimer, < 0.5 ng/mL) and inflammation (CRP, 1.5 mg/L), liver enzymes (aspartate aminotransferase, 19 U/L; alanine aminotransferase, 15 U/L; lactate dehydrogenase, 112 U/L), and cardiac enzymes (creatine kinase (CK), 60 U/L; CK-MB, 12.0 U/L; high-sensitivity troponin I, 0.001 ng/mL; N-terminal prohormone of brain natriuretic peptide, 65 pg/mL). Chest X-ray was unremarkable (Figure 1). The 12-lead electrocardiogram (ECG) was in order (Figure 2). The patient was diagnosed with dyspnea, and inhaler with a fixed combination of anticholinergic agent and beta 2 adrenergic agent and theophylline were prescribed; he was then referred for further examination.

Transthoracic echocardiography (TTE) revealed standard heart structure, function, and blood flow through all chambers and valves with the left ventricular ejection fraction of 65%, without any signs of diastolic dysfunction, pulmonary hypertension, or pleural effusion. To assess left ventricle (LV) diastolic function,[5] we performed two-dimensional and Doppler measurements (Table), including mitral E/A ratio (Figure 3A), septal E/e′ ratio (Figure 3B), peak TR velocity (Figure 3C), and left atrial volume (Figure 3D). Endocrinological examination was regular, and nasal fiberoptic laryngoscopy ruled out vocal cord dysfunction. Complete neurological examination was unremarkable, and no pathological changes have been observed on the multidetector computed tomography (CT) of the endocranium.

Three months after the mild COVID-19, all previously reported symptoms were still present, without any improvement after initiating the prescribed pulmonary therapy. Arterial blood gas revealed mild hypocapnia with respiratory alkalosis (pH 7.48; partial carbon dioxide pressure, 4.1 kPa; partial oxygen pressure, 12 kPa; bicarbonate, 20 mEq/L), suggesting hyperventilation. Spirometry testing (forced expiratory volume in 1 second (FEV1), 110%; forced vital capacity (FVC), 108%; FEV1/FVC ratio, 80%) showed no changes in small airways, mostly ruling out asthma. Lung diffusion capacity for carbon monoxide was performed, and the value was in the reference range (> 80%). Lung ultrasonography was normal (12-zone score, 0/12), interpreted per COVID-19 lung ultrasonography protocol (Figure 4).[6] All 6-minute walk test (6-MWT) parameters were in the reference range (distance, 520 m; oxygen saturation, 96%; Borg scale, 0.5), according to current guidelines.[7] Normal findings were also observed on high-resolution CT (HRCT), without consolidations or "ground-glass" opacities (Figure 5A), whereas CT pulmonary angiogram did not show any signs of pulmonary embolism (Figure 5B). Considering no cardiorespiratory condition has been diagnosed during comprehensive follow-up diagnostic protocol, our differential diagnosis included anxiety-related dysfunctional breathing.

Therefore, psychiatric exploration has been conducted. During the interview, mild anxiety has been observed in our patient, including health concerns and disturbances in concentration. The patient also reported that he slept poorly in the previous period and often woke up during the night. As part of mental health assessment, the patient filled out Beck's scale for anxiety and depression,[8,9] the Generalised Anxiety Disorder 7-Item Scale,[10] and the Insomnia Severity Index Scale,[11] after signing the inform consent. Scale scoring revealed mild anxiety and severe insomnia. Psychiatric evaluation revealed that our patients' observed anxiety level was unlikely the leading cause for the respiratory symptoms he experienced but certainly may be a participating factor. The initiated thera-

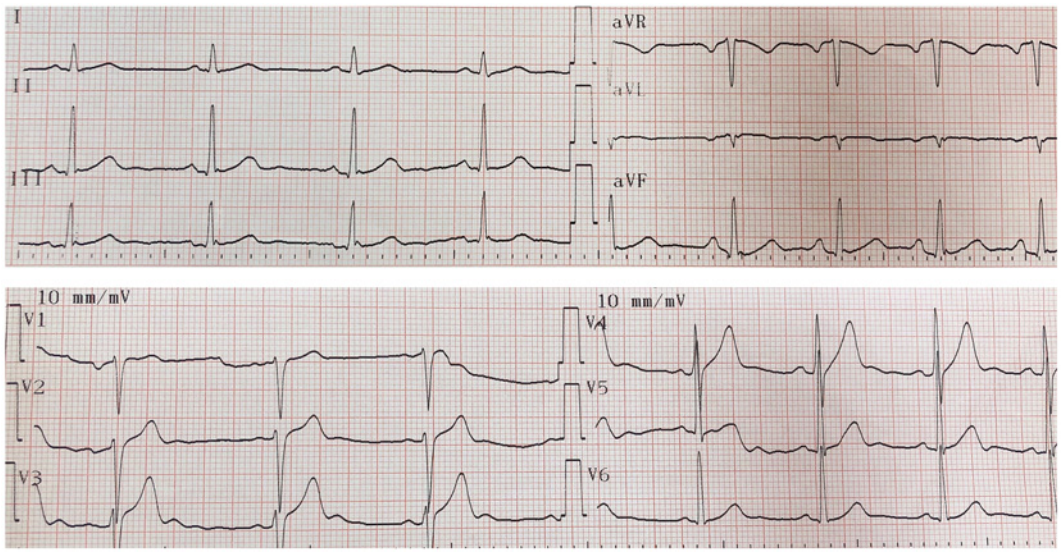

Figure 2. Twelve-lead ECG with no pathological findings.

Table. TTE Parameters for the Assessment of LV Diastolic Function in Our Patient

Parameters	LAVI (mL/m^2)	Mitral E/A ratio	Septal E/e'	Deceleration time (m/second)	Peak TR velocity (m/second)	Septum thickness (mm)
Obtained values	21.6	1.28	5.3	180	2.3	10

TTE indicates transthoracic echocardiography; LV, left ventricle; LAVI, left atrial volume index; and TR, tricuspid regurgitation.

peutic protocol involved the use of benzodiazepines and hypnotics, and a psychiatric checkup was planned for two weeks, or earlier if necessary.

To resolve the origin of unexplained dyspnea, we referred our patient to the reference facility to perform a cardiopulmonary exercise test (CPET). The CPET was performed according to the Bruce treadmill protocol, because bike ergometer was not available and, also, this was a good way to test dyspnea on exertion in a patient in whom no other cause of dyspnea has been previously defined. The test duration was 8 minutes when terminated before achieving maximal effort (respiratory exchange ratio (RER), ≥ 1.10) due to a sudden onset of severe exercise-limiting dyspnea (RER, 1.0). Reduced exercise capacity (VO_2 peak, 28 mL/kg/minute; 68% from predictive value) was obtained. BP values were within normal ranges at rest, with an inadequate increase at exercise peak (220/110 mmHg). No arrhythmias, ventricular repolarization abnormalities, and signs of myocardial ischemia were detected. Respiratory pattern analysis during exercise revealed impaired ventilatory efficiency (VE/VCO_2 slope, 32.4) (Figure 6A) with increased VE peak value (100 L/minute) in the presence of preserved breathing reserve (42%) (Figure 6B). Of note, ventilatory equivalents reached slightly increased values (VE/VO_2 peak, 30; VE/VCO_2 peak, 33) (Figure 6C). During the test, end-tidal oxygen tension ($PetO_2$) and end-tidal carbon dioxide tension showed normal response with sudden decrease at the time of dyspnea ($PetO_2$, 98 versus 109 mmHg; $PetCO_2$, 41 versus 36 mmHg). A good anaerobic threshold (26.8 mL/kg/minute) precludes deconditioning as a cause of dyspnea (Figure 6D). The VO_2/HR showed a good response of 23 mL/beat but reached an early plateau. However, the test lasted very short after the VAT, which indicated low tolerance for higher efforts. Also, there was an inadequate increase of BP during the exercise, which can be a sign of uncontrolled hypertension (220/110 mmHg) and thus, a potential cause of masked left ventricular diastolic dysfunction[12-15] presented with dyspnea, impaired VE/VCO_2 slope, and $PetCO_2$, in the presence of reduced $PeakVO_2$ and regular VAT (VO_2) values. Considering other factors, this patient is overweight, with a BMI of 29.4 kg/m^2, which is associated with hypertension and may be a cause of dyspnea in exertion. Finally, CPET confirmed diastolic dysfunction as the most probable cause of unexplained dyspnea in our patient who had COVID-19. Further therapy included beta-blockers and angiotensin-II receptor blockers.

Discussion

In this paper, we report an interesting case of a male with unexplained post-COVID-19 dyspnea. During the comprehensive follow-up diagnostic protocol, CPET revealed left ventricular diastolic dysfunction unmasked by COVID-19.

The effects of COVID-19 are numerous, and so are the consequences. One meta-analysis revealed that pulmo-

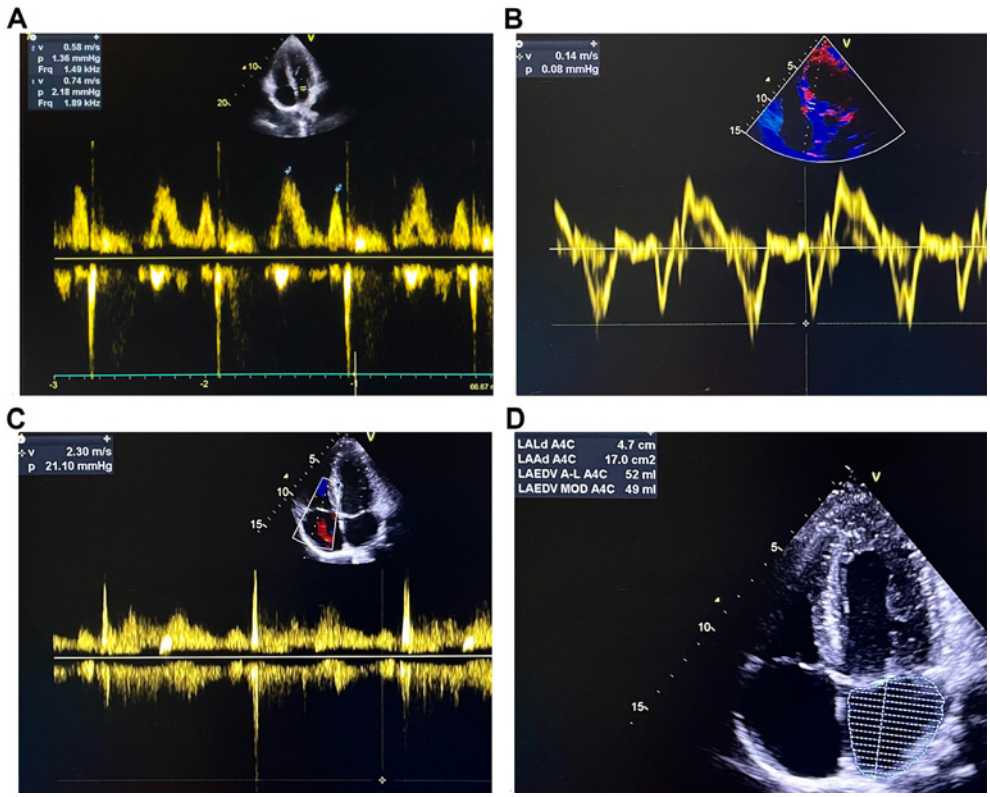

Figure 3. **A:** TTE examination of flow velocity across the mitral valve (E/A ratio in normal range) in the apical four chamber view using pulse wave Doppler. **B:** TTE examination of mitral annular velocities obtained using tissue Doppler (e´ = 0.14 m/second). **C:** TTE examination of flow velocity across the tricuspid valve (TR velocity in normal range) in the apical four chamber view using continuous wave Doppler. **D:** TTE examination of LA volume in 2D mode in the apical four chamber view.

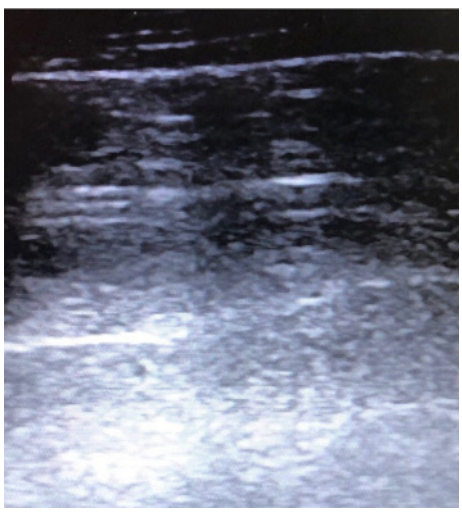

Figure 4. Transthoracic lung ultrasound (A lines, lung sliding) (normal findings).

nary sequelae, such as altered diffusion capacity and obstructive and restrictive patterns, were present in 39%, 7%, and 15% of patients with COVID-19, respectively.[16] The autopsies of patients with COVID-19 showed different degrees of pulmonary interstitial fibrosis and destruction in the alveolar structure.[17] These structural and functional changes are followed by a different degree of symptoms in the post-COVID period, with fatigue, dyspnea, and joint and chest pain as the most frequent ones.[18] Bearing this in mind, the need to follow-up these patients and perform lung CT is recommended by clinical guidelines.[19] Our patient experienced recurrent breathlessness during physical exertion and periodical fatigue even two months after the infection, but despite common post-COVID-19 pulmonary sequelae, his structural and functional pulmonary testing was normal. Therefore, while basic diagnostics elucidated no cardiopulmonary pathology, psychogenic reasons as a cause of unexplained dyspnea in our patient were also considered.

One of the recent guidelines on COVID-19 follow-up pointed out the great importance of holistic assessment and management of various conditions in patients who had COVID-19, including dysfunctional breathing and anxiety. The comprehensive follow-up diagnostic protocol in our case included a multidisciplinary approach and several diagnostic tools, including pulmologic, cardiologic, endocrinologic, otorhinolaryngologic, neurologic, and psychiatric evaluation. Both psychiatric clinical examination and Beck's scale for anxiety demonstrated that our patient suffered from mild anxiety, which might point to anxiety-

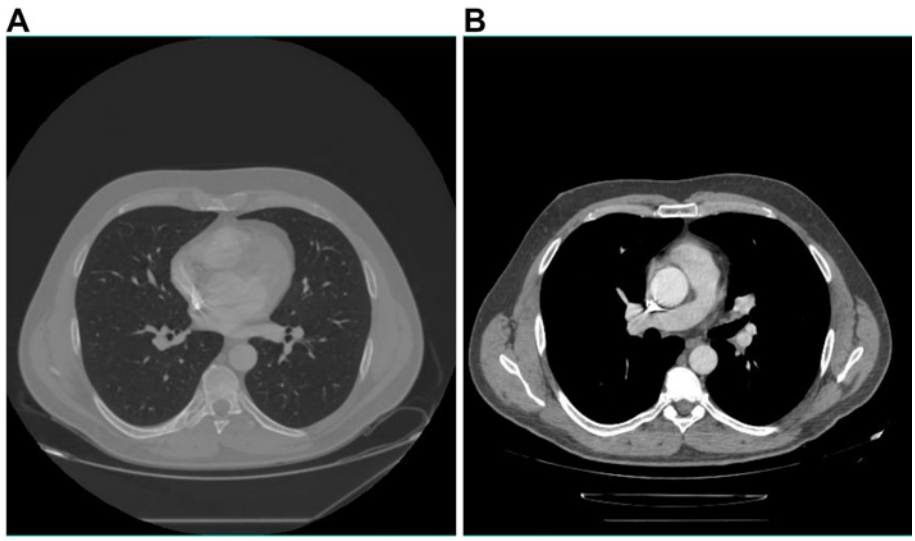

Figure 5. **A:** HRCT (normal findings). **B:** CT pulmonary angiogram (normal findings).

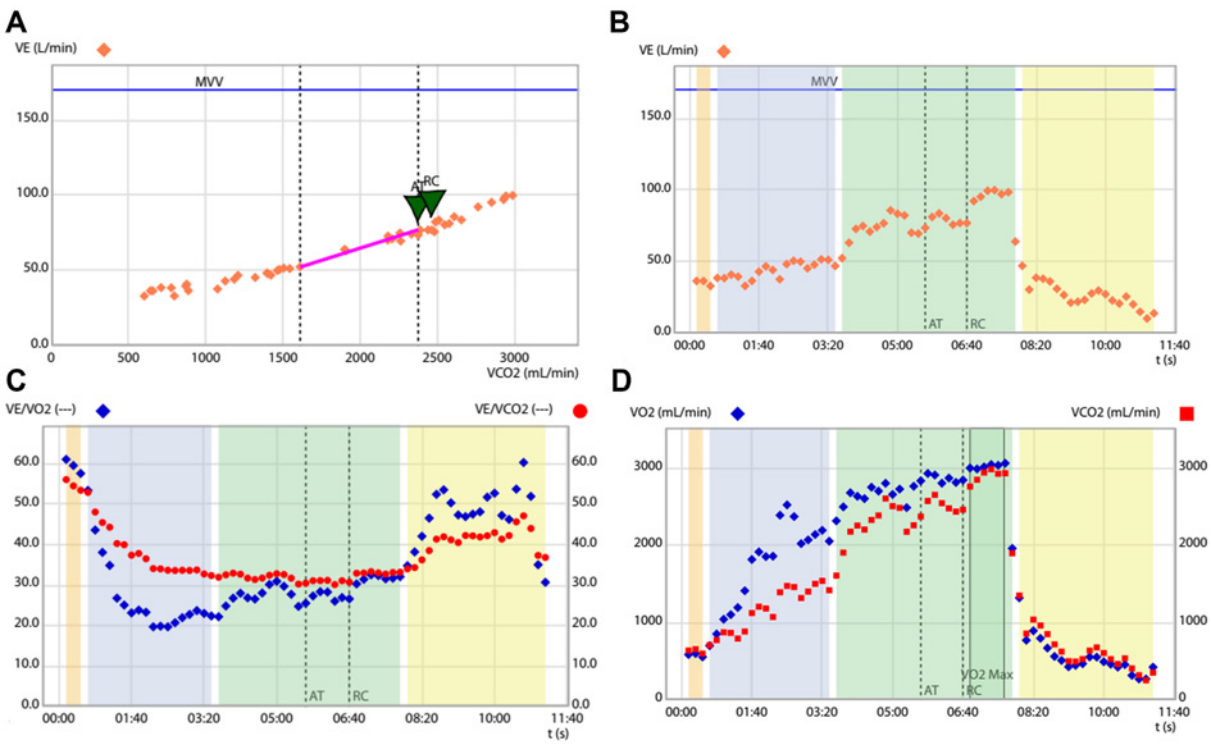

Figure 6. **A:** CPET showing impaired ventilatory efficiency (VE/VCO_2 slope, 32.4). **B:** CPET showing increased VE peak value (100 L/minute) in the presence of preserved breathing reserve (42%). **C:** CPET showing ventilatory equivalents that reached slightly increased values (VE/VO_2 peak, 30; VE/VCO_2 peak, 33). **D:** CPET showing reduced exercise capacity (VO_2 peak, 28 mL/kg/minute; 68% from predictive value of peak VO_2) and acceptable lactic threshold (VAT) (63% from value of peak VO_2).

related dysfunctional breathing at first sight. The higher prevalence of psychiatric disorders, such as anxiety, insomnia, depression, and posttraumatic stress disorder (42%, 40%, 31%, and 28%, respectively) has already been demonstrated among survivors of COVID-19.[20] Furthermore, our patient had the symptomatology that favors dysfunctional breathing,[4] which is a complex disorder characterized by intermittent/chronic breathing irregularity, manifesting as dyspnea, exercise-induced breathlessness, deep sighing, often yawning, hyperventilation-induced hypocapnia, and additional complaints such as fatigue, lightheadedness, or anxiety.[21] Although this condition is mainly associated with cardiopulmonary disorders (secondary dysfunctional breathing), when there is no confirmation of

any somatic disease, it may be related to anxiety-related conditions (primary dysfunctional breathing).[22]

However, considering the lack of adequate definition and gold standard diagnostics for dysfunctional breathing and its frequent overlapping with commonly accompanied cardiopulmonary disorders, such as a heart failure (HF) and asthma,[23] we decided to perform the CPET. Generally, the role of CPET in determining early HF stages is evolving,[24] and in the case of unexplained dyspnea, CPET may detect its origin by evaluating the cardiopulmonary reserve.[23] Although the impaired ventilatory response on CPET stands for the most common feature of diastolic dysfunction,[12] in addition to impaired VE/VCO2 slope, our patient also had decreased VO2 peak. Finally, in comparison to resting echocardiography, spirometry testing, and 6-MWT, initially performed in our patient, the CPET revealed diastolic dysfunction, which confirmed its superiority in assessing unexplained dyspnea. Recent studies showed that the E/e′ ratio, as the most reliable Doppler measure of LV filling at rest, lacks the robust clinical evidence for the estimation of left ventricular filling pressure during exercise.[25] They also propose CPET and exercise stress echocardiography as they can more precisely identify alterations at the root of the effort intolerance.[25] However, our patient had no CPET before COVID-19 infection, so we couldn't compare parameters, which represents a limitation of this interesting case; however, a control after 6 and 12 months could yield more information.

The emerging data of COVID-19 and long-term myocardial complications have been reported. It is recently observed that COVID-19 may exacerbate preexisting, unmask the subclinical, or provoke the new onset of HF with preserved ejection fraction (HFpEF).[26] Although there remains no enough evidence whether SARS-CoV-2-related myocardial injury and inflammation arise from its direct myocardial damage or systemic immunological inflammation, COVID-19 and HFpEF share similar inflammatory pathophysiology and cardiometabolic risks. Since hypertension is recognized as one of the major causes of HFpEF,[27] in our case, the coexistence of untreated hypertension and excessive body weight could be an excellent base for HFpEF development.

Conclusion

According to the current evidence, we may suggest that, before SARS-CoV-2 infection, our patient had subclinical and asymptomatic HFpEF, which was triggered by COVID-19 and clinically manifested. The CPET may be a useful method for resolving these diagnostic dilemmas, as in our case. Further studies should provide more extensive evidence concerning SARS-CoV-2 and HFpEF, which would undoubtedly facilitate the timely recognition and therapy initiation in this patient population.

Disclosure

Conflicts of interest: All authors declare no conflict of interest.

Informed consent: The statement of informed consent for publication was obtained from the patient in accordance with the COPE guidelines.

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