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# Exercise Intolerance and Excessive Chronotropic Response Due to Possible Autonomic Dysfunction Post COVID-19 Infection

**Stefanos Archontakis[1], Dimitrios Venetsanos[1], Nikias Milaras[1], Eirini Beneki[1], Panagiotis Dourvas[1], Epameinondas Triantafyllou[1], Konstantinos Sideris[1], Konstantina Aggeli[2], Petros Arsenos[2], Athanasios Kordalis[2], Konstantinos Gatzoulis[2], Skevos Sideris[1]***

[1]Department of Cardiology, Hippokration General Hospital, Athens, Greece
[2]First Cardiology Division, Hippokration General Hospital, Medical School, University of Athens, Athens, Greece
Email: *skevos1@otenet.gr

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## Abstract

**Introduction and Objectives:** In patients with Post-Acute Sequelae of Coronavirus 2 infection (PASC), a post infectious autonomic dysfunction may be one of the underlying mechanisms. Patients often present with exercise intolerance and exaggerated heart rate response to exercise. We report a single centre experience of patients with PACS and suspected autonomic dysfunction. **Methods:** Forty-two patients evaluated in the Outpatient Cardiology Department with suspected PASC were included in the study. Patients complained of compromised exercise performance persisting >3 months after recovery from COVID-19 infection, compared to the pre-COVID-19 period. The patients were evaluated with 12-lead electrocardiogram, echocardiography, 24-hour ECG ambulatory monitoring and either exercise stress test or a 6-minute walk test. **Results:** All 42 patients demonstrated an exaggerated chronotropic response, defined as the inappropriate increase in heart rate before the 6$^{th}$ minute of exercise >100% of the age-predicted maximal heart rate value with reproduction of clinical symptoms. In addition, 24-hour ambulatory electrocardiography revealed an increased mean heart rate of 92 beats/minute and decreased mean standard deviation of sequential 5-minute N-N interval (SDNN) of 74.4 ms. Pharmaceutical treatment with b-blockers, ivabradine or both was administrated in 29 (69%) resulting in symptomatic improvement in 82.8% of those under treatment. However, residual symptoms persisted in 69% of patients after 3 months. **Conclusions:** In patients

with "Post-acute COVID-19" syndrome, we found an excessive chronotropic response to exercise suggesting autonomic dysfunction as the underlying mechanism of symptoms. Treatment with beta blockers or ivabradine resulted in clinical improvement but a substantial proportion of patients remained symptomatic.

## Keywords

COVID-19, Autonomic Neuropathy, Exertional Intolerance, Exaggerated Chronotropic Response, POTS, Dysautonomia

## 1. Introduction

Over 630 million cases of SARS CoV-2 (SARS CoV-2) infection had been confirmed on November 2022, since the beginning of the pandemic, representing a significant challenge for health systems worldwide [1]. In addition to the short-term increased mortality and morbidity rates in these patients, recent studies revealed an increased incidence of symptoms persisting for weeks or months following acute infection, often referred to as Post-Acute Sequelae of Coronavirus 2 infection (PASC) or "long COVID-19" [2]. Symptoms such as fatigue, headache, postural tachycardia, orthostatic intolerance, dizziness and cognitive impairment, palpitations, gastrointestinal dysfunction and exercise intolerance presumed to represent the long-term effect of the disease [2] are identified in 10% - 20% of COVID-19 infection survivors [3]. For most of these manifestations, autonomic dysfunction appears to be one of the underlying mechanisms, especially in patients presenting with orthostatic intolerance, POTS, neurocardiogenic syncope or orthostatic hypotension [4] [5] [6], especially in the case of Orthostatic Intolerance and Postural Orthostatic Tachycardia Syndrome (POTS) [7]-[13].

## 2. Objectives

In the present case series, we report a single centre experience of diagnostic and therapeutic management of patients with suspected PACS.

## 3. Methods

This retrospective study was performed in a single centre in Greece. Informed consent was obtained from each patient. In addition, the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by our institution's human research committee. Cases were collected retrospectively after reviewing the outpatient clinic database for the time-period between May 2021 and April 2022.

Patients were either self-referred or referred to our outpatient clinic by their healthcare provider for cardiovascular evaluation following COVID-19 infec-

tion. Inclusion criteria were: 1) fully asymptomatic patients prior to COVID infection, 2) the presence of exercise intolerance persisting >3 months post COVID-19 recovery, and 3) recording of an exaggerated chronotropic response. Patients with pre-existed cardiac disease, implantable cardiac devices, uncontrolled hypertension, or other serious medical condition were excluded.

Basic cardiovascular assessment included obtaining a thorough medical history and physical examination, laboratory tests (including full blood count, biochemistry, and thyroid function tests), 12-lead electrocardiogram (ECG) and echocardiogram in all cases. Next, patients underwent either a treadmill exercise stress test (EST) (45.2%) or a 6-minute walk test to assess the functional status more accurately. Tilt Table Test was performed in 2 cases and where appropriate a 10-min stand test was performed to assess orthostatic intolerance (n = 20). In addition, all 42 patients underwent a 24-hour ambulatory electrocardiographic assessment.

Details obtained from the medical record included demographics, medical history, laboratory investigations, radiological findings (chest radiograph and/or computed tomography, CT), cardiovascular assessment tests, clinical management and patient outcome and survival.

Autonomic dysfunction was indicated by the presence of excessive increase in heart rate upon standing accompanied by orthostatic intolerance or by the presence of an abnormally high resting heart rate higher than 100 bpm or by recording a disproportional increase of heart rate compared to the status of exercise. When clinically relevant, the presence of POTS, defined as the orthostatic increase of the heart rate (HR) of >30/min (>40/min in patients of 12 - 19 years of age) in the absence of concomitant blood pressure drop in patients with duration of symptoms of orthostatic intolerance for at least 3 months, was assessed.

COVID-19 infection was confirmed by positive reverse transcription-polymerase chain reaction results on respiratory samples.

## 4. Results

The records of forty-two patients (37 female) fulfilling the above-mentioned inclusion criteria were further investigated. Demographic data are presented in Table 1. Median age was 41.2 ± 11.3 years (range: 26 - 66 years). All patients were older than 20 years of age, whereas 11 were between 21 and 30 years old, 10 were between 31 and 40 years old, 11 were between 41 and 50 years old, 7 were between 51 and 60 years old and 3 were older than 61 years. Three male patients were between 31 and 40 years old, 1 was between 41 and 50 years old, whereas 2 were between 51 and 60 years old. Mean time-period between COVID-19 infection and 1st appointment was 3.7 months. Prior to COVID-19 all patients were fully functional and asymptomatic without significant co-morbidities. Thirty-nine of the 42 patients were fully vaccinated, whereas 3 were not vaccinated.

During COVID-19 infection, 28 patients presented with mild symptoms of acute respiratory infection, 10 patients reported moderate symptoms such as

**Table 1.** Demographics of the patient study group.

| | N = 42 (%) |
|---|---|
| **Age** (years old) | 41.2 ± 11.3<br>Range: 26 - 66 |
| **Sex** | |
| • Female | 37 (88.1%) |
| • Male | 3 (11.9%) |
| **Risk factors** | |
| • Arterial Hypertension | 9 (21.4%) |
| • Diabetes Mellitus | 2 (4.8%) |
| • Dyslipidaemia | 9 (21.4%) |
| • Smoking | 14 (33.3%) |

high fever lasting for >3 days, breathlessness and coughing whereas 4 patients were diagnosed with pneumonia, however none of the patients was hospitalised. Nine patients reported anosmia and/or ageusia.

All patients were referred to our Outpatient Department for exercise intolerance at mild exertion and a significant impairment of their quality of life, persisting at least 3 months after recovery from COVID-19 infection. Other symptoms were fatigue (69%), palpitations during exercise (76.2%), syncope (14.3%), presyncope (23.8%) and postural intolerance (26.2%) without fulfilling the diagnostic criteria of POTS (Table 2).

Twenty-four patients had a respiratory assessment prior to their visit in our department whereas the rest were referred to respiratory clinic by us to rule out a respiratory condition associated with their symptoms. All patients underwent a chest x-ray (n = 33) and/or chest computerised tomography (n = 24).

Following the assessment scheme (Figure 1), we did not reveal structural heart disease in any case in this group of patients, based on the clinical, electrocardiographic, and echocardiographic findings. On the other hand, we revealed an exaggerated chronotropic response defined as the inappropriate increase in heart rate before the 6$^{th}$ minute of exercise >100% of the age-predicted maximal heart rate value (APMHR) in all 42 patients with reproduction of clinical symptoms. In addition, 24-hour ambulatory electrocardiography revealed an increased mean heart rate and a decreased mean standard deviation of sequential 5-minute N-N interval (SDNN) of 74.4 ms (range: 52 - 112 ms) (Table 3, Figure 2).

Twenty-nine patients (69%) received pharmacotherapy for the treatment of the presumed autonomic dysfunction attributed to the post-acute sequelae of COVID-19 infection which included beta blockers, (n = 16), either Metoprolol (75 - 125 mg/day) or Bisoprolol (10 mg/day), or ivabradine 5 mg bid (n = 11) or a beta-blocker/ivabradine combination (n = 2). Thirteen patients did not wish to receive medication after reassurance, and remained on non-pharmacological measures only.

All 42 patients had a regular follow-up 1 month and 3 months after the initial

**Table 2.** Clinical symptoms.

| Symptom | N (%) |
|---|---|
| *Exertional Intolerance* | 42 (100%) |
| *Orthostatic Intolerance* | 11 (26.2%) |
| *Fatigue* | 29 (69%) |
| *Palpitations* | 32 (76.2%) |
| *Pre-syncope* | 10 (23.8%) |
| *Syncope* | 6 (14.3%) |

**Table 3.** Diagnostic and therapeutic interventions.

| Intervention | N (%) |
|---|---|
| **History/Physical Examination** | 42 (100%) |
| **Assessment at Respiratory Department** | |
| • Referral to Respiratory Department | 18 (42.8%) |
| • Referral from Respiratory Department | 24 (57.2%) |
| **Pulmonary Imaging** | |
| • Chest X-ray | 33 (78.6%) |
| • Chest Computerised Tomography (CT) | 24 (57.1%) |
| **Laboratory Tests** (full blood count/liver function tests/blood glucose/thyroid function tests/renal function tests) | 42 (100%) |
| **Electrocardiogram** | 42 (100%) |
| **Echocardiogram** | 42 (100%) |
| • Mean Ejection Fraction: | 62% |
| **24-hour ambulatory ECG-recording** | 42 (100%) |
| • Mean SDNN | 74.4 ms (range: 52 - 112 ms) |
| • Mean Heart Rate | 92 beats/minute |
| **Functional status assessment** | |
| • Exercise Stress Test | 19 (45.2%) |
| • 6-Minute Walk Test | 23 (54.8%) |
| **Orthostatic Test** | 20 (47.6%) |
| **Tilt Table Test** | 2 (4.8%) |
| **Pharmaceutical Therapy** | 29 (69%) |
| • b-blockers | 16 (38.1%) |
| • Ivabradine | 11 (26.2%) |
| • b-blockers/ivabradine combination | 2 (4.8%) |
| **Response to treatment** | 24/29 patients (82.8%) |
| **Residual symptoms** | 29/42 patients (69%) |

assessment. Most patients (69%) reported residual symptoms 3 months after the first visit in our department. However, in most of the cases (24 of 29 patients, 82.8%), patients showed a significant improvement with treatment, reporting a

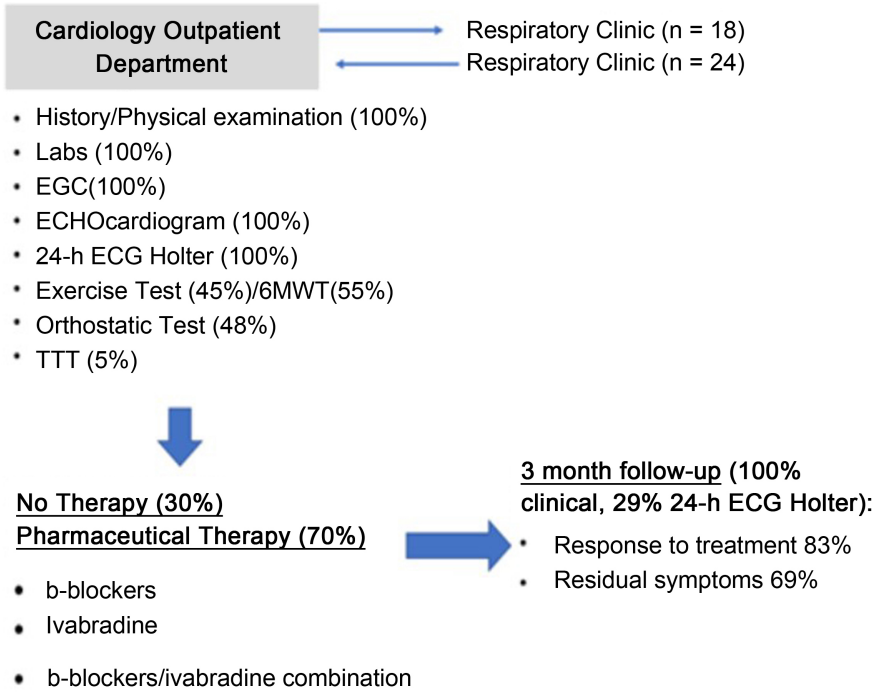


**Figure 1.** 24-hour ambulatory electrocardiographic recording of a 33 years-old female patient with exertional intolerance persisting 3.5 months after recovery of COVID-19 infection.

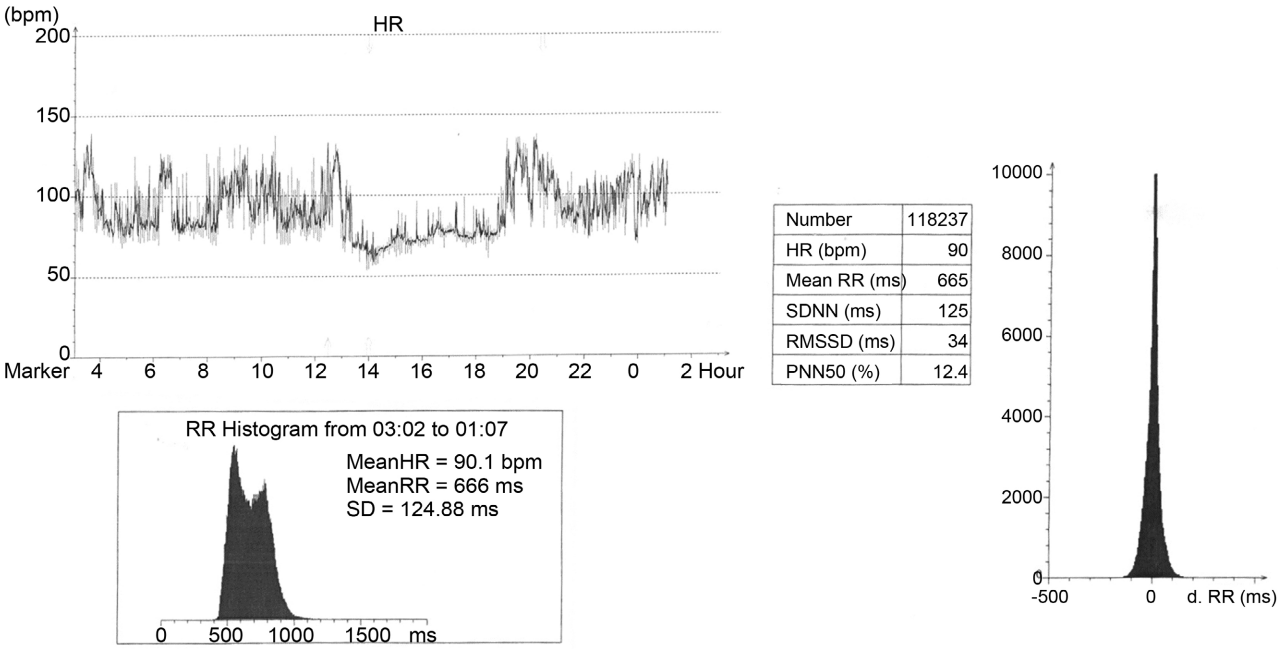


**Figure 2.** 24-hour ambulatory electrocardiographic recording of a 52 years-old female patient with exertional intolerance persisting 3 months after recovery of COVID-19 infection.

better functional status and quality of life. Beta-blocker/ivabradine combination was effective and significantly reduced symptoms. Moreover, ivabradine administration resulted in a significant improvement in 10 of the 11 patients. Beta-

blockers were effective in 12 of the 16 patients. No significant side effects or significant variations in response among individuals was recorded. Interestingly, a 24-hour ambulatory ECG test was repeated in 12 patients (28.6%) showing a significant decrease in mean heart rate compared to the subject's 24-hour Holter performed during the initial assessment.

## 5. Discussion

Various neurologic manifestations have been described in patients previously infected by SARS CoV-2 virus [2]. Among those, several disorders of the Autonomic Nervous System such as POTS may occur in previously healthy individuals. Symptoms may persist for weeks after recovery from the acute infection and are encompassed in the so-called "Post-acute COVID-19" or "long COVID-19" syndrome [7] [9] [11] [14] [15] [16]. Many symptoms of post-acute COVID syndrome appear to be autonomic in nature, suggesting that autonomic impairment may play a central role in the underlying patho-physiology [17]. Some authors suggest that a combination of orthostatic tachycardia and symptoms such as dyspnoea or palpitations, persisting in the post COVID-19 infection period, may indicate the presence of POTS [2] [11]. In a large case series, authors reported that POTS and other common autonomic disorders can follow COVID-19 in previously healthy non-hospitalized patients who experience significant disability 6 - 8 months after an acute infection [10].

In the present study, we specifically detected and retrospectively investigated a group of patients presenting in the Outpatient Cardiology Department with persistent symptoms of exercise intolerance after COVID-19 infection, who were proved to manifest an exaggerated chronotropic response. All patients were previously healthy and reported long-lasting symptoms, in most of the cases fatigue and palpitations during mild to moderate exercise, post-acute COVID-19 infection recovery, severely decapacitating their quality of life. In general, physical exercise increases oxygen demand and subsequently leads to increased heart rate due to an enhanced sympathetic activity and an inhibition of the parasympathetic limb. On the other hand, an excessive rise in heart rate, in the post-COVID period in previously healthy and asymptomatic patients, may represent a possible autonomic imbalance resulting from sympathetic hyperactivity as well as a reduced vagal activity. In this situation, heart rate reaches its peak early, resulting in limitation of maximum exercise capacity.

In the present study we used two methods to assess the presence of excessive chronotropic response to physical activities, namely traditional treadmill exercise testing in 45% and 6-minute walk test in 55% of the patients. In all cases the APMHR was reached before the 6$^{th}$ minute of exercise, with reproduction of clinical symptoms. Therefore, based on the clinical and diagnostic findings we may assume that these patients represent a group with an autonomic imbalance variant presenting with exercise intolerance due to an excessive chronontropic response. We believe that these findings may suggest an underlying autonomic

dysfunction due to the COVID-19 infection. Clinical symptoms may be classified in the spectrum of "Post-acute COVID" entity, since symptomatology onset was closely related to it.

Patients were highly symptomatic and sought for medical advice despite of the fact that none required hospitalization. Therefore, our data suggest that even mild cases of COVID-19 infection can lead to "Post-acute COVID" symptoms.

Furthermore, 24-hour ECG recording recorded an increased mean HR of 92 beats/minute indicating, presumably, a worst autonomic balance with increased chronotropic response to exercise. In addition, SDNN (standard deviation of normal-to-normal R-R intervals), an essential variable of heart rate variability measures, is considered as the "gold standard" for medical stratification of cardiac risk when recorded over a 24 h period, predicting both morbidity and mortality. In our study, mean SDNN was calculated at 74.4 ms with a range of 52 - 112 ms, indicating a deteriorated Heart rate Variability.

Several studies demonstrate that a rapid HR increase at the beginning of a standard EST is a strong and independent predictor of cardiac death and non-fatal myocardial infarction in patients with coronary artery disease as well as heart failure, probably via an increase in electrical instability and thus enhancing life-threatening arrhythmias [18] [19]. On the other hand, a prospective study recruiting 149 patients did not find evidence of excess cardiovascular risk in COVID-19 survivors, after a 6-month follow-up period, compared to patients who had no history of the disease [20]. Similarly, in our study, no death was recorded, and most of the patients reported an improvement in symptoms after a 3-month follow-up period.

Recently, investigators highlighted the phenomenon of abnormal sinus tachycardia in patients previously infected by SARS CoV-2 virus, and proposed that "post-COVID-19 tachycardia syndrome" should be considered a phenotype or sub-syndrome of post-acute COVID-19 syndrome [21]. Post-COVID-19 tachycardia syndrome may represent a POTS or inappropriate sinus tachycardia subset contributing to several symptoms in this patient group [21]. Furthermore, Aranyo *et al*., recently, reported that Inappropriate Sinus Tachycardia (IST) is prevalent among post-acute COVID-19 patients. In their study, among 200 patients, 40 (20%) fulfilled the diagnostic criteria for IST, namely a symptomatic sinus rhythm rate ≥ 100 bpm at rest with a mean 24-h heart rate above 90 beats/min in the absence of any acute physiological demand or conditions known to commonly produce sinus tachycardia [22] [23]. Additionally, IST was accompanied by a decrease in most heart rate variability parameters such as pNN50 and HF band, whereas the disorder was more common in young women without previous comorbidities and with mild SARS-CoV-2 infection [22]. Authors, suggest that cardiac Autonomic Nervous System imbalance with decreased parasympathetic activity seems to be a plausible pathophysiological explanation for this phenomenon [22]. Due to the similarities in the demographics of our patient group as well as the findings of the 24-hour ambulatory electrocardio-

graphic assessment, it can be speculated that IST may also be the diagnosis, at least, in a subset of our patients. However, a significant difference with our study is that in this patient group (that also included mostly young or middle age women), individuals had a persistently increased heart rate, whereas in our study, patients had a predominantly exaggerated heart rate response to exercise, and symptoms occurred mostly during exercise. The exact mechanisms leading in these dysautonomic subtypes remain to be investigated in future research. however clinical doctors should recognise and treat them at an early stage.

Medical therapy was initiated in 29 of the 42 patients, however in the total group of the 42 patients 69% reported residual symptoms 3 months after the first visit. Nevertheless, 83% of the patients who received medical treatment reported a significant improvement. Beta blockers and/or ivabradine was initiated in a dose depending on the 24-hour ambulatory electrocardiography results, and was further increased according to patient's symptoms. Beta-blocker/ivabradine combination or ivabradine monotherapy administration appear to be more effective compared to b-blocker monotherapy, however the patient sample is small, and no definite conclusions can be extracted. Even though there is not a uniform approach to managing cardiac dysautonomias, pharmacologic agents should be prescribed as adjuncts to existing non-pharmacological therapies on a case-by-case basis. Non-pharmacological measures include patient education (*i.e.* avoiding triggers and activities that might aggravate their symptoms, performing counter-pressure maneuvers), increase in water and salt intake to promote volume expansion, avoiding medication that reduces blood volume or decreases blood vessel tone (such as antihypertensives, diuretics and nitrates), using compression garments that reach the abdomen to enhance venous return and attending exercise training programs introduced gradually to avoid aggravating symptoms and slowly progress from non-upright activities (e.g. rowing machines, recumbent cycles) to upright aerobic exercises.

Autonomic dysfunction is not rare in those affected by COVID-19, and patients are often highly symptomatic with a severely compromised quality of life in the short and probably in the long term. A better understanding of the complex and various pathophysiological mechanisms that affect the autonomic nervous system as well as an early recognition of the dysautonomia subtypes and administration of medical treatment at an early stage could help reduce the sequelae of COVID-19.

The study has several limitations. First of all, this is a retrospective, non-randomised, single centre case series report and therefore results must be evaluated from this perspective. In addition, the size of the sample population studied is small comprising of only 42 patients. The population of this study is, additionally, restricted to those patients who sought medical assistance due to their symptoms at the Cardiology Outpatient Department of our hospital, and therefore findings cannot be expanded to the general population or to all COVID patients. Moreover, long-term follow-up is absent. Presence of long-term follow-up data remains a critical aspect of this type of research since only a few data exist in li-

terature regarding long-term prognosis of dysautonomias as well as the exact mechanisms leading to persisting symptoms. Therefore, future research should incorporate extended observation periods. Fourth, the symptom-limited maximal exercise test or 6-minute walk test that was used to assess the patients' functional status may be influenced by several factors. This strategy does not provide information regarding the metabolic and oxygen demand during exercise. Fifth, the presence of an autonomic disorder is only speculated and is not proven by autonomic laboratory testing, neither patients assessed in specialized neurology departments in order to confirm diagnosis. Sixth, an exaggerated chronotropic response was defined as the inappropriate increase in heart rate before the 6$^{th}$ minute of exercise >100% of the age-predicted maximal heart rate value (APMHR) with a concomitant reproduction of clinical symptoms. This definition, although clinically relevant for this specific patient group, is arbitrary. In addition, a 10-min stand test was only performed in 20 patients, when considered to be clinically relevant (such as in the case of reported orthostatic intolerance or syncope), leading in inhomogeneity in the diagnostic procedure. A Tilt Table test may be considered for patients assessed for POTS. On the other hand, an active stand test is a simple evaluation for POTS (and orthostatic hypotension) that can be done at the bedside or in the clinic with only an automated or manual BP cuff and therefore, most authors consider it as being the standard of care for assessing patients with orthostatic complaints [24] [25]. However, the inhomogeneity in the diagnostic procedure, including patients not assessed for orthostatic intolerance, patients assessed with Tilt Table Test and patients assessed with a 10 minutes active stand test, may have compromised the results of the present study. Finally, improvement in symptoms was not recorded with a repeated exercise test or 6-minute walk test.

## 6. Conclusion

In this retrospective study of patients recovered from SARS CoV-2 virus infection, we identified a subgroup of patients with "Post-acute COVID-19" syndrome with exercise intolerance due to excessive chronotropic response. Our findings provide more evidence on the mechanism of, at least, a subset of patients with "Post-acute COVID" symptoms, suggesting the presence of autonomic dysfunction. Although that, in most cases, this is a temporary, gradually resolving phenomenon, clinical doctors should suspect and diagnose this variety of PASC in patients with a previous COVID-19 infection complaining for exercise intolerance.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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