


# Impact of COVID-19 lockdown on exercise capacity in PAH patients

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## Abstract

The outbreak of novel coronavirus-19 disease (COVID-19) was classified as a global pandemic thanks to the rapid viral spread, and restrictive policy measures of infection containment, including “lockdown” periods and self-isolation, were first instituted in Belgium from March to June 2020. The consequent reduction in physical activity could have a negative impact on exercise capacity, especially in frail patients with pre-existing chronic diseases, such as pulmonary arterial hypertension (PAH). With the aim to define the impact of COVID-19 lockdown on functional status, we included in our observational analysis clinically stable PAH patients, who had performed at least four consecutive 6-min walking tests (6MWT) during 2019–2020, to compare their exercise performance before and after the lockdown. In the 63 patients included, a comparison between the distance covered at 6MWT after the lockdown period and the pooled mean of the previous three 6MWTs showed a mean reduction of 14 m after the lockdown ( $p = 0.004$ ). Moreover, the mean distance covered at 6MWT went from 447 m in March 2020 to 434 m in June 2020, with a significant average loss of 13 m ( $p = 0.024$ ). Our results showed that PAH patients were less performing at 6MWT after 3 months of reduced physical activity, despite constant clinical stability and the absence of signs of disease progression, suggesting that this confounding factor should be kept in mind when evaluating changes in 6MWT during or after COVID-19 pandemic.

## KEYWORDS

6MWT, COVID-19, exercise, lockdown, pulmonary arterial hypertension

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The outbreak of novel coronavirus-19 disease (COVID-19) was declared a “Public Health Emergency of International Concern” by the World Health Organization and was classified as a global pandemic in March 2020.<sup>1</sup> The combination of significant morbidity and rapid spread of the virus has led to restrictive policy measures, including the decision of “lockdown” periods aiming to slow the transmission of the infection. Containment measures involving a social distancing, quarantine with self-isolation, and advice on “stay at home,” started on March 2020, and were gradually being lifted as of June 2020.<sup>2,3</sup>

These policy restrictive measures, although necessary, were believed to be negatively counterbalanced by a reduction of exercise levels in the population, with physical deconditioning and loss of muscle mass and strength.<sup>2,4</sup> This was confirmed by recent analyses, highlighting the detrimental effect of the lockdown period on physical activity and promoting sedentary behavior also in healthy subjects.<sup>2,5</sup>

Patients with pre-existing chronic diseases, such as pulmonary arterial hypertension (PAH), were considered more difficult to manage in case of COVID-19 infection. Accordingly, they were prompted to carefully reduce individual infection risks, minimize social interactions, and adopt stricter containment measures, meaning that physical activity in this group might have been even further reduced in comparison with the general population.<sup>6</sup>

Therefore, it is conceivable that deconditioning could have significantly impacted the exercise capacity of patients with PAH, and might act as a confounding factor in the evaluation of their functional status.

To test this hypothesis, the present report shares clinical data from an observational analysis of 6-min walking tests (6MWT) performed before and after the lockdown period in PAH patients followed at our center.

We included clinically stable PAH patients, who had performed at least four consecutive 6MWT during 2019–2020. Patients with hospitalization, clinical worsening, and/or modification of PAH-specific therapy during the last 2 years were excluded, as well as those with less than four 6MWT from January 2019 to November 2020. We considered the three 6MWT measurements performed right before (March 2020) and the measurement right after (June 2020) the lockdown period in our analysis.

Linear mixed models were used to analyze the 6MWT, heart rate, oxygen saturation, and Borg score observed at different visits including a random effect for each patient considering potential differences between individuals using an unstructured variance-covariance matrix. Specific contrasts were built to test

the hypotheses about a difference between the mean of three measurements prelockdown and the mean measurement at the visit postlockdown as well as the difference between measurement at the visit immediately before lockdown and the one postlockdown. These contrasts were evaluated considering a type I error of 0.025 to control the inflation of the type I error. A paired *t*-test (or Wilcoxon signed-rank sum test in case of no normal data) was used to investigate the difference pre- and postlockdown of the following continuous variables: weight, N-terminal pro-brain natriuretic peptide (NTproBNP), tricuspid annular plane systolic excursion (TAPSE), and right atrial area. Cohen  $\kappa$  and its 95% confidence interval (CI) were implemented to test the concordance pre- and postlockdown of the New York Heart Association (NYHA) functional class and the presence of pericardial effusion. All analyses are performed using SAS 9.4 (SAS Institute).

Out of 111 PAH patients who had performed a 6MWT before and after the lockdown period, we excluded four patients due to therapeutic changes, and 42 patients with less than four tests during 2019 and 2020.

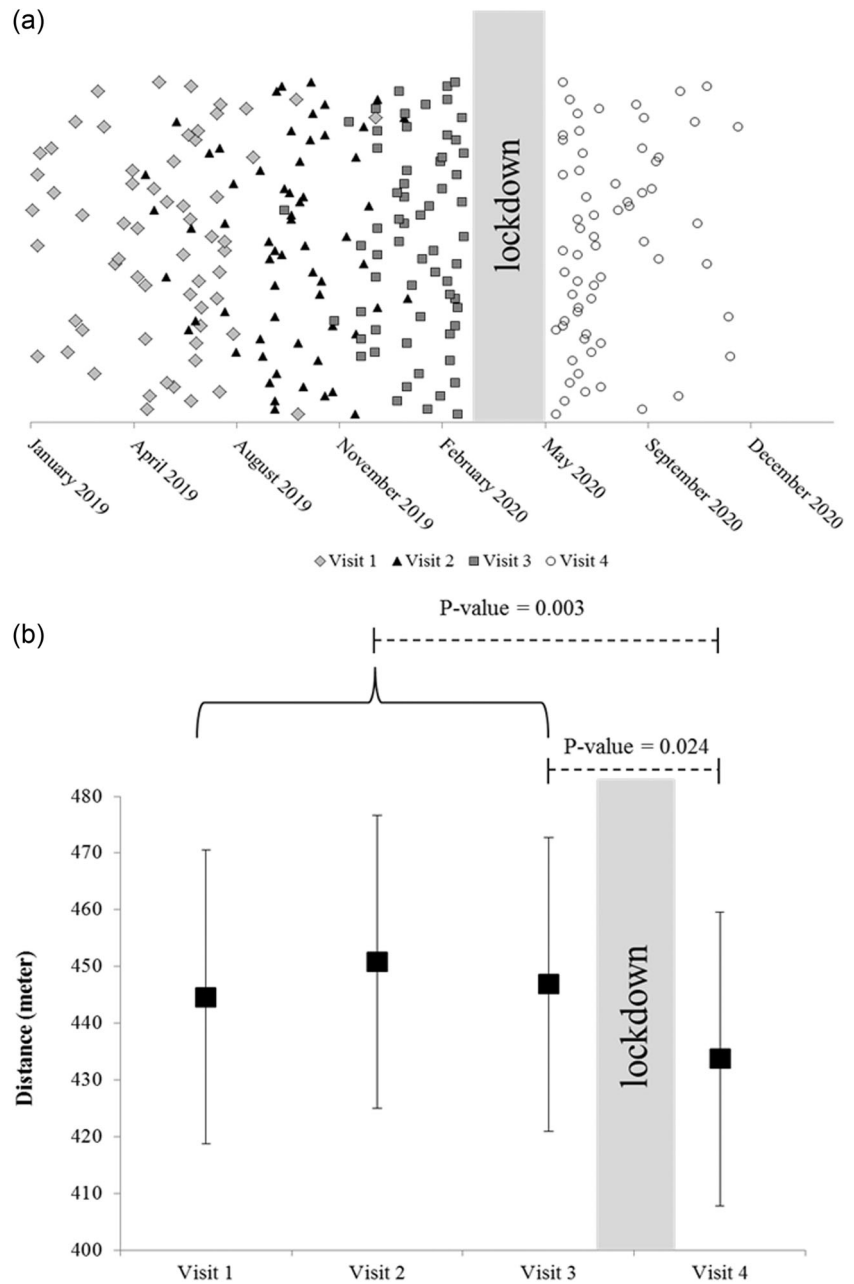
The final population was composed of 63 patients with quarterly evaluations in the last 2 years in stable clinical conditions. Idiopathic, heritable, and drug-induced PAH was the most prevalent etiology, accounting for 60% of the population. Other etiologies were PAH due to congenital heart disease (11 patients), PAH associated with connective tissue disease (6 patients), portopulmonary hypertension (5 patients), PAH associated with HIV (2 patients), and pulmonary venoocclusive disease (1 patient). No patients included in the analysis got COVID-19 infection during the period of the study.

Most patients were in specific PAH combination therapy, either double (57%) or triple (29%), with more than half of the latter on intravenous prostacyclin. Almost all patients complained of exertional dyspnea NYHA Class II (66%) or III (31%), while 3% were asymptomatic (NYHA Class I).

Figure 1 represents the trend in time of 6-min walk distance (6MWD) of our population from January 2019 to November 2020, showing a relative constancy in 6MWD from January 2019 to March 2020 and a clear drop in the exercise performance since June 2020.

A comparison between the 6MWD after the lockdown period and the pooled mean of the previous three 6MWDs showed a mean reduction of 14 m ( $p = 0.004$ ) after the lockdown. The mean distance covered at 6MWT went from 447 m in March 2020 to 434 m in June 2020, with a significant average loss of 13 m ( $p = 0.024$ ), highlighting a decrease in exercise capacity likely due to the lockdown.

**FIGURE 1** (a) Distribution over time of the four 6MWT (Visits 1–4) performed by patients from January 2019 to December 2020. 6MWTs were not performed during the lockdown period (i.e., March–June 2020). (b) 6MWD (mean and 95% confidence interval) for each visit is reported, as well as the statistical comparison. 6MWD, 6-min walk distance; 6MWT, 6-min walking tests.



This abrupt reduction in physical performance was also maintained in the 3–6 months following the end of the lockdown period, as witnessed by the distance covered in the two tests performed after the end of the lockdown period, equal to was  $436 \pm 14$  (based on 53 patients) and  $405 \pm 14$  (based on 46 patients) m, respectively.

In contrast, the other variables collected during the 6MWT, were not different just before and immediately after the lockdown (heart rate: difference = 1.37 bpm,  $p = 0.4749$ ; oxygen saturation: difference =  $-0.68\%$ ,  $p = 0.2912$ ; Borg score: difference =  $-0.06$  points,  $p = 0.8040$ ).

Moreover, noninvasive parameters indicative of disease progression suggested no significant change before and after the lockdown period. In particular, a good concordance between periods was observed for NYHA functional class ( $\kappa$ : 0.86 [95% CI: 0.75–0.97]) as well as between median levels of weight (median [interquartile range]: 71 [58–82] vs. 73 [55–82] kg,  $p = 0.716$ ), NTproBNP (129 [64–225] vs. 190 [73–294] pg/ml,  $p = 0.511$  – available only in one-third of patients) and echocardiographic characteristics including the right atrial area (19.9 [16.3–23.1] vs. 19.5 [16.9–23.5] cm<sup>2</sup>,  $p = 0.804$ ), TAPSE (20 [17–23] vs. 20 [18–23] mm,  $p = 0.664$ ). Analogously, high concordance was observed for the presence of

pericardial effusion ( $\kappa$ : 0.84 [0.62–1]). Additionally, no patient experienced hospitalizations or escalations in medical therapy after the lockdown period.

Our results suggest that the COVID-19 lockdown period significantly impacted exercise tolerance in patients affected by PAH. Indeed, despite constant clinical stability and the absence of signs of disease progression, PAH patients were less performing at 6MWT after 3 months of reduced physical activity. A similar heart rate and symptom perception for a lower 6MWD after lockdown, in the presence of stable right heart function, quite strongly points to deconditioning as the major cause of exercise limitation. Additionally, the deleterious effects of deconditioning seemed to persist thereafter, as witnessed by the stable reduction of 6MWD over time.

6MWT is a reproducible, inexpensive, easily interpretable, and routinely executed test that measures exercise tolerance, and is considered an indicator of the ability to perform activities of daily life.<sup>7</sup> However, our results may suggest that the distance walked during a 6MWT performed after the lockdown period should be viewed with caution, both in the context of the global risk stratification that drives treatment strategies as well as in the context of Phase 2–3 clinical trials where 6MWT is a classical endpoint.<sup>8,9</sup> In PAH, regular physical activity and physical training have been shown significantly improve quality of life, functional class, and the distance walked during 6MWT.<sup>10–12</sup> It has also been previously reported that a lower day-to-day physical activity was associated with more self-reported mental and physical fatigue, as well as less exercise tolerance in PAH patients and that these correlate with the performance at 6MWT.<sup>12,13</sup>

Nonetheless, the reduction in the distance walked during a 6MWT that we could demonstrate might not be considered clinically meaningful. Indeed, a recent meta-analysis showed an average difference of 22.4 m in delta 6MWD favoring active treatment over placebo, which was considered clinically relevant.<sup>14</sup> However, 6MWD should be thought of as a continuum, and in such a context it would seem important from a clinical perspective to maintain stability in exercise performance over time. Indeed, a threshold value in 6MWD reduction to define a significant worsening in clinical profile secondary to a brutal interruption of physical activity has not been defined yet.<sup>8</sup>

We acknowledge that the retrospective nature of this single-center observational study is a limitation to be considered while interpreting our findings, together with limited access to our facility during the lockdown period. This situation was unavoidable, however, given the severity of the pandemic in our Region.

In summary, the COVID-19 lockdown period may have resulted in significant physical deconditioning and seems to have had a relevant impact on the functional

capacity of clinically-stable ambulatory PAH patients. Although the clinical meaning of this functional worsening is not yet clear, this confounding factor may have an influence on 6MWD interpretation and should be kept in mind when evaluating changes in 6MWD during or after the COVID-19 pandemic.

## AUTHOR CONTRIBUTIONS

**Claudia Baratto:** Conceptualization, data curation, investigation, methodology, and writing – original draft. **Céline Dewachter:** Conceptualization, data curation, methodology, supervision, and writing – review and editing. **Sergio Caravita:** Conceptualization, methodology, supervision, and writing – review and editing. **Antonella Zambon:** Methodology, formal analysis, and writing – review and editing; **Antoine Bondue:** Supervision and writing – review and editing. **Gianfranco Parati:** Supervision and writing – review and editing. **Jean-Luc Vachiéry:** Conceptualization, methodology, supervision, and writing – review and editing.

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## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

## ETHICS STATEMENT

The need for written informed consent was waived due to the retrospective nature of the study.

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