Dysfunctional breathing symptoms, functional impact and quality of life in patients with long COVID-19: a prospective case series

Léon Genecand 1,2,3, Marco Altarelli 1,4, Alzbeta Binkova 1,4, Selina Loew 1,4, Stéphanie Vaudan 1,5, Grégoire Gex 1,4, Pierre-Olivier Bridevaux 1,3,4, Isabelle Frésard 1,4

ABSTRACT
Background Dysfunctional breathing is increasingly recognised after SARS-CoV-2 infection, but the associated symptoms, functional impact and quality of life have not been systematically studied.

Methods This study describes a prospective case series of 48 patients with dysfunctional breathing based on compatible symptoms and an abnormal breathing pattern during cardiopulmonary exercise testing. Patients with underlying disease that could explain these symptoms were excluded. Median time from COVID-19 to evaluation was 212 (IQR 121) days. Self-administered questionnaires, including the Nijmegen questionnaire, Short-Form (SF-36) Health Survey (SF-36), Hospital Anxiety and Depression Scale, modified Medical Research Council scale, post-COVID-19 Functional Scale, and specific long COVID symptoms, were the outcome measures.

Results On average, mean V'O₂ was preserved. Pulmonary function tests were within limits of normality. Hyperventilation, periodic deep sighs/erratic breathing and mixed types of dysfunctional breathing were diagnosed in 20.8%, 47.1% and 33.3% of patients, respectively. After dyspnoea, the five most frequent symptoms using the Nijmegen scale with a cut-off of ≥3 were faster/deeper breathing (75.6%), palpitations (63.8%), sighs (48.7%), inability to breathe deeply (46.3%) and yawning (46.2%). Median Nijmegen and Hospital Anxiety and Depression Scale scores were 28 (IQR 20) and 16.5 (IQR 11), respectively. SF-36 scores were lower than the reference value.

Conclusions Long COVID patients with dysfunctional breathing have a high burden of symptoms, functional impact and a low quality of life, despite no or negligible organic damage.

INTRODUCTION
Dyspnoea frequently persists after SARS-CoV-2 infection, independent of abnormalities on chest imaging or pulmonary function tests (PFTs) and initial disease severity. Deconditioning and respiratory limitation (RL) evaluated by cardiopulmonary exercise testing (CPET) are the main exercise-limiting factors after severe SARS-CoV-2 necessitating hospitalisation. However, the mechanisms of persisting dyspnoea after uncomplicated mild SARS-CoV-2 infection are poorly understood. One possible mechanism could be dysfunctional breathing (DB), defined as dyspnoea associated with an abnormal breathing pattern after exclusion of a significant cardiopulmonary disease that could cause dyspnoea, or dyspnoea occurring out of proportion with an underlying cause (eg, cardiopulmonary or metabolic diseases and deconditioning) and associated with an abnormal breathing pattern. DB may cause symptoms at rest and during various daily life situations, including exercise. Different types have been described with hyperventilation syndrome (HVS) and periodic deep sighing (PDS) identified as the most common subtypes. In the classification by Boulding et al, PDS encompasses frequent...
sighs as well as erratic breathing (EB). Here, we use the term EB/PDS to describe this combination of abnormal breathing patterns.\(^9\) Given its complex features, there is currently no gold standard for the diagnosis of DB.\(^9\)

Although the Nijmegen Questionnaire was validated as a tool to detect subjective symptoms associated with HVS,\(^10\) its lack of diagnostic accuracy has been acknowledged.\(^10\)\(^11\) In addition, its use has been extrapolated to other types of DB, but lacks a rigorous validation.\(^9\) CPET has been recently recommended as an attractive tool for the diagnosis of DB as it provides evidence of abnormal breathing patterns and allows the exclusion of significant cardiopulmonary disease-limiting exercise.\(^11\)\(^12\) Thus, a combined approach using formal symptom assessment and CPET is recommended for the diagnosis of DB.\(^11\)

As DB is associated with diverse respiratory and non-respiratory symptoms, it could explain some persisting symptoms often described in long COVID patients, such as chest tightness, sensation of restriction during inspiration, chest pain and paresthesia.\(^13\) HVS has been described in a case series of patients following SARS-CoV-2 infection and was further suspected in a larger patient population.\(^14\)\(^15\) EB/PDS was described as the second type of possible DB following SARS-CoV-2.\(^16\)\(^17\) A significant burden of symptoms associated with DB in long COVID patients has been described in a small number of patients, but it has not been systematically quantified so far.\(^14\) Our objective was to describe the symptoms, quality of life (QoL) and functional outcome using subjective and objective measures in a large case series of long COVID patients having DB.

**METHODS**

**Study population**

We present the initial results of an ongoing, prospective, case series study conducted in two major Swiss regional hospitals to investigate the evolution of patients 6–9 months after the diagnosis of new onset DB following SARS-CoV-2 infection (ClinicalTrials.gov: NCT05217875). The strengthening the reporting of observational studies in epidemiology (STROBE) statement was followed when applicable (online supplemental table S1). We included adolescents (aged 15 or older) and adults diagnosed with DB at our long COVID outpatient clinic. DB was diagnosed based on the following combined approach: the presence of compatible symptoms, including a significant dyspnoea defined by a modified Medical Research Council (mMRC) score ≥1, combined with other symptoms related to DB (ie, symptoms from the Nijmegen Questionnaire, for example, chest tightness, chest pain, palpitations, deep sighs, yawning) and the presence of an abnormal breathing pattern (HVS, EB/PDS or a mixed pattern) during CPET evaluation, with the exclusion of pathologies that could fully explain these symptoms. Only patients with a PCR-confirmed SARS-CoV-2 infection were included. Patients with adequately controlled asthma or minimal interstitial sequelae after COVID-19 not causing RL (ventilatory limitation or gas exchange abnormalities as defined in online supplemental material 1 during CPET evaluation were also included. Exclusion criteria were acute COVID-19 infection within the preceding 6 weeks, clinically relevant interstitial disease after COVID-19 as evidenced by RL during CPET, significant cardiorespiratory diseases that could alter the ventilatory pattern, and CPET not meeting quality control criteria (ie, gas leaks or patients unable to follow instructions).

**Clinical setting**

Patients were referred to the long COVID ambulatory clinic by primary care physicians due to persistent symptoms or for a follow-up visit after hospital admission due to acute COVID-19. Prior to the visit, patients completed a specific questionnaire to obtain the following data: symptoms at the time of the visit and at the time of acute infection; date of test for SARS-CoV-2 detection; hospitalisation status; occurrence of complications during or after infection; referral to ambulatory/stationary rehabilitation after infection; need of supplemental oxygen; administration of a treatment during the acute phase; comorbidities; smoking status; current medication; level of physical fitness before COVID-19 and whether this was reduced post-COVID; and profession. Based on the questionnaire, patients were allocated to four levels of physical activity prior to SARS-CoV-2: sedentary, mild, moderate and intense.

All patients completed the Hospital Anxiety Depression Scale (HADS), the Short Form 36 Health Survey (SF-36) and the post-COVID Functional Scale (PCFS).\(^18\)\(^19\)\(^20\) The Nijmegen Questionnaire was administered at the discretion of the clinician.\(^10\) Severity of acute COVID-19 disease was assessed according to the WHO classification.\(^21\) All patients complaining of persistent dyspnoea were systematically evaluated as follows: complete PFTs (Geratherm Respiratory, Blue Cherry platform software, Bad Kissingen, Germany), including spirometry with bronchodilatation, static lung volume measurements and single breath carbon monoxide transfer capacity (TLCO) performed by a trained physician; chest X-ray; ECG; blood analysis including complete blood count, electrolytes and N-terminal prohormone of brain natriuretic peptide (NT proBNP) and CPET, including rest and peak exercise measurements of arterial blood gases. Other tests (eg, metacholine provocation test) or specific evaluations (eg, ear, nose, throat) were ordered if clinically appropriate to exclude conditions such as asthma, post-COVID interstitial and vascular sequelae or laryngeal functional dysfunction. We used the most recent Global Lung Initiative reference equations for spirometry, static lung volume and TLCO.\(^22\)\(^23\)\(^24\)

**CPET evaluation**

Incremental CPET was performed on a cycle ergometer following the 2019 statement of the European Respiratory
Society on the standardisation of CPET in pulmonary disease. Our study-specific CPET protocol has been published elsewhere and is detailed in the supplementary material. The Study of Health in Pomerania reference equations were used to compare observed results with predicted values. For determination of the objective maximal effort, we used the equations suggested in the 2019 European Respiratory Society statement. The DB pattern according to CPET findings was classified into three categories: EB/PDS without HVS; HVS without EB/PDS; and a mixed type of HVS and EB/PDS. During CPET, other associated limitations/abnormalities were analysed and categorised: O₂ delivery/utilisation impairment, RL, metabolic limitation, chronotropic insufficiency, arrhythmia and ischaemia. Definitions of limitations and the analysis of the DB pattern are provided in online supplemental material 1. In summary, objective criteria using mainly V'E/V'CO₂ slope were used to diagnose HVS. Subjective evaluation of irregularity of breathing using unfiltered graphs and continuous volume-time as well as flow-volume graphs were used to diagnose EB/PDS.

**Patient and public involvement**

Public was not involved in the design or planning of the study. Patients were involved in the design of the study. We invited three patients of the case series to read an advanced draft of the manuscript. We asked them about areas missed or not sufficiently emphasised. Topics that were particularly important for them were the impact on QoL, functional repercussion and work capacity. We accordingly added details on these topics. The physiopathological explanation of their condition was also important for them. Even though the physiopathology is far from being completely understood, we added a physiopathological hypothesis about DB in the context of long COVID. Available treatment was also a concern for these patients and should be the scope of future studies.

**Statistics**

Normally distributed data were reported as means (SD) and compared by Student’s t-test or one-way analysis of variance. Non-normally distributed data were reported as medians (IQR) and compared by the Mann-Whitney U test or the Kruskal-Wallis rank sum test. Ordinal data were reported as percentages and compared by Fisher’s exact test or χ² test as appropriate. A p≤0.05 was considered statistically significant. Missing data are reported in online supplemental table S2. Statistical analyses were performed with R software (V.3.6.2).

**RESULTS**

From 1 March 2021 to 31 October 2021, 264 patients were evaluated. Among these, 48 (female, 68.8%; mean age, 48.5 (SD, 15.0) years) were included in the study (figure 1). Baseline characteristics of patients are shown in table 1. In general, patients were previously healthy, never smoked (68.8%) and had mild severity acute COVID-19 (WHO severity score 1 (70.8%)). In most cases, hospitalisation was not required (85.4%). Before COVID-19, 12.5%, 39.6%, 33.3% and 14.6% of patients were sedentary, mildly, moderately or intensively active, respectively. Most patients (93.6%) did not report dyspnoea before COVID-19 and had an mMRC score of 2 (42.6%) or 3 (34.0%) at the time of the visit. Median delay between diagnosis and clinical evaluation with CPET was 212 (IQR 118) days. Patients with EB/PDS had a more frequent history of asthma (7/22 (31.8%)) than other subgroups (0% in HVS and mixed type, p=0.008) (online supplemental table S3).

Table 2 shows the general symptoms at the time of the initial visit. Patients exhibited a high burden of variable symptoms affecting breathing, cognition, mood and muscular function (median number of reported symptoms, 12 (IQR 6)). The mixed type and hyperventilation groups reported loss of appetite more frequently (37.5% and 44.4%, respectively) compared with the EB/PDS group (9.1%) (p=0.035). The mixed type group reported a more frequent weight loss (43.8%) compared with the other two subgroups (p=0.009). Symptoms were otherwise similar between groups (online supplemental table S4).

Table 3 shows the most frequently selected items of the Nijmegen Questionnaire (≥3 points). After dyspnoea, the five main selected items were faster or deeper breathing (75.6%), palpitations (63.8%), sighs (48.7%), unable to breathe deeply (46.3%) and yawning (46.2%); 68.9% of patients had a total Nijmegen score ≥23 points. The Nijmegen mean total score did not differ between the three groups of diagnosed DB (EB/PDS, HVS, mixed) (online supplemental table S5). Table 4 summarises the SF-36, HADS and PCFS scores. SF-36 QoL scores were low, especially in the domains of physical functioning, vitality, social functioning and emotional role. The SF-36 score of DB patients stratified by gender contrasted with healthy never-smokers of a comparable age in Switzerland and showed an important decrease in the QoL score compared with age-matched controls (figure 2). 62.5% of patients had a high risk for anxiety and/or depression (HADS≥15). Almost all (97.9%) patients had functional repercussions related to COVID-19. Among these, 31.9% reported a PCFS of 2 (equivalent to the presence of limitations in everyday life that lead to the avoidance/reduction of usual duties/activities due to symptoms, pain, depression or anxiety), and 40.4% a PCFS of 3 (incapacity to perform some usual duties/activities due to symptoms, pain, depression or anxiety, but without the need of external help). Patients with a mixed type were significantly more impaired than other subgroups (75% with a PCFS of 3 (online supplemental table S6). Otherwise, there was no significant difference in HADS, SF-36 and PCFS scores between groups.

Table 5 shows PFTs, CPET and arterial blood gases before and after exercise. On average, PFTs were within
No individual had obstructive spirometry (defined as an FEV1/FVC < −1.64 Z score). One patient had a restrictive pattern (defined as a TLC < −1.64 Z score). Five patients had an abnormal TLCO (defined as a TLCO < −1.64 Z score). Using predetermined criteria, CPET were maximal in 42 patients (87.5%) with an average normal peak V' O2 of 87% and a normal predicted peak work of 92%. The V'E/V'CO2 slope was higher in the HVS group and mixed group (38.9 and 36.4, respectively) compared with the EB/PDS group (24.9). The HVS group had a normal mean pH (7.37) at the end of exercise, despite a high lactate (8.6 mmol/L) due to a relatively low end-exercise PaCO2 (3.7 kPa) representing disproportionate hyperventilation. Laboratory tests and radiological examinations were within reference values for most patients (table 6). An abnormal NT proBNP was found in 1 patient (2.2%). Chest CT or chest X-ray identified abnormalities in five patients (four post-COVID-19 lung interstitial anomalies of a limited extent and one segmental pulmonary embolism).

**DISCUSSION**

Our study found that previously healthy, long COVID patients diagnosed with DB lived with a high burden of...
symptoms, poor QoL and a high level of post-COVID functional impact, despite a long delay between acute COVID-19 infection and assessment (median, 7 months). The clinical impact of long COVID-associated DB is worrisome. First, the long delay between the acute infection and assessment suggests an ongoing active process. Second, there is currently no therapy for long COVID-associated DB that has proved effective in controlled trials. Third, the working and living capacity of long COVID patients with DB may be durably reduced, posing a societal problem given the high number of individuals infected by SARS-CoV-2. To our knowledge, this study analysed the largest case series of long COVID patients diagnosed with new onset DB. DB was diagnosed in 32.4% of our ambulatory patients presenting with unexplained dyspnoea and this finding adds to the growing evidence that it seems to be a common condition among long COVID patients.14–17 In addition, we provide a detailed assessment of symptoms, QoL and functional repercussions.

Our findings showed that in addition to dyspnoea, the five most frequently selected items from the Nijmegen scale were faster or deeper breathing, palpitations, sighs, inability to breathe deeply and yawning. Other symptoms reported by more than 50% of patients were fatigue, myalgia, trouble sleeping, chest tightness, headache, vertigo, change of mood, memory loss, concentration difficulties and cough. Compared with the measured value in a similar control group of healthy never-smokers in Switzerland,29 SF-36 scores were markedly reduced in most domains, largely more than the minimal clinical important difference (MCID) of 10 points,19 suggesting not only an important physical impact with limiting
symptoms, but also a significant impact in multiple QoL domains. The low SF-36 scores in our study are preoccupying as it has been shown in population and clinical studies that reduced physical functioning, chronic pain and reduced mental health were strongly associated with the working disability rate.\textsuperscript{30,31} The functional impact was high with a PCFS of 2 and 3 in most patients (73.9%), representing either a limitation or an impossibility to perform some daily tasks/activities. Together with poor QoL, high PCFS scores in a middle-aged population of previously active workers with only initial mild infection may be an important concern for the long-term work capacity of long COVID patients with DB.

More than 60% of patients with DB exhibited severe anxiety and/or depression symptoms. Anxiety and depression could be the consequences of DB, but also contributing factors to DB. Indeed, anxiety disorders have been linked to DB.\textsuperscript{3} In this context, the exact number of symptoms, functional repercussions and impact on QoL that can be attributed to DB, anxiety or depression is unclear.

However, we think that the most important aspect is not to fully understand the causality between these different conditions, but to recognise that anxiety and depression are frequent in patients diagnosed with DB and should be systematically screened. This offers clinicians the possibility to have a multimodal approach with their patients, targeting both the DB with specific physiotherapy and the anxiety/depression if present with both non-pharmaceutical and pharmaceutical approaches.

Although patients with EB/PDS reported a history of asthma more frequently, this association might be spurious in the context of multiple subgroup analyses. In this case series, patients were predominantly female which is in concordance with data showing the female sex is a risk factor for persisting symptoms after SARS-CoV-2 infection.\textsuperscript{32}

The physiopathology of DB after SARS-CoV-2 remains to be elucidated, but an active process affecting the respiratory centres might be present. Importantly, recent data showed that even mild COVID was associated with changes in brain structure, including brainstem mass loss.\textsuperscript{36} Of note, a large majority of our patients reported neurocognitive symptoms, with 85.1% and 78.7% reporting difficulty focusing and forgetfulness,

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Symptoms at first consultation</th>
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<tbody>
<tr>
<td></td>
<td>Dysfunctional breathing (N=48)</td>
</tr>
<tr>
<td>No of reported symptoms, median (IQR)*</td>
<td>12.0 (6)</td>
</tr>
<tr>
<td>Symptoms, n (%)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>45 (95.7)</td>
</tr>
<tr>
<td>Difficulty focusing</td>
<td>40 (85.1)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>40 (85.1)</td>
</tr>
<tr>
<td>Trouble sleeping</td>
<td>39 (83.0)</td>
</tr>
<tr>
<td>Forgetfulness</td>
<td>37 (78.7)</td>
</tr>
<tr>
<td>Chest oppressions</td>
<td>32 (68.1)</td>
</tr>
<tr>
<td>Headache</td>
<td>32 (68.1)</td>
</tr>
<tr>
<td>Vertigo</td>
<td>30 (63.8)</td>
</tr>
<tr>
<td>Palpitations</td>
<td>30 (63.8)</td>
</tr>
<tr>
<td>Change of mood</td>
<td>29 (61.7)</td>
</tr>
<tr>
<td>Cough</td>
<td>25 (53.2)</td>
</tr>
<tr>
<td>Dyspnoea at rest</td>
<td>23 (48.9)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>17 (36.2)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>16 (34.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>15 (31.9)</td>
</tr>
<tr>
<td>Rhinorrhoea</td>
<td>12 (25.5)</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>12 (25.5)</td>
</tr>
<tr>
<td>Sore throat</td>
<td>12 (25.5)</td>
</tr>
<tr>
<td>Cutaneous redness</td>
<td>12 (25.5)</td>
</tr>
<tr>
<td>Sputum</td>
<td>12 (25.5)</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>10 (21.3)</td>
</tr>
<tr>
<td>Loss of weight</td>
<td>10 (21.3)</td>
</tr>
<tr>
<td>Anosmia</td>
<td>9 (19.1)</td>
</tr>
</tbody>
</table>

*Median number of symptoms experienced by patients at first consultation from the list below.

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Nijmegen score at time of diagnosis of dysfunctional breathing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dysfunctional breathing (N=48)</td>
</tr>
<tr>
<td>Nijmegen score, total, median (IQR)</td>
<td>28 (20)</td>
</tr>
<tr>
<td>Nijmegen score, total, ≥23, yes, n (%)</td>
<td>31 (68.9)</td>
</tr>
<tr>
<td>Nijmegen items scoring ≥3 points, yes, n (%)</td>
<td></td>
</tr>
<tr>
<td>Faster or deeper breathing</td>
<td>31 (75.6)</td>
</tr>
<tr>
<td>Palpitations</td>
<td>30 (63.8)</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>29 (72.5)</td>
</tr>
<tr>
<td>Unable to breathe deeply</td>
<td>19 (46.3)</td>
</tr>
<tr>
<td>Tight feelings in chest</td>
<td>17 (41.5)</td>
</tr>
<tr>
<td>Feeling tense</td>
<td>16 (39.0)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>16 (39.0)</td>
</tr>
<tr>
<td>Bloated stomach feeling</td>
<td>15 (37.5)</td>
</tr>
<tr>
<td>Cold hands or feet</td>
<td>14 (34.1)</td>
</tr>
<tr>
<td>Tingling fingers</td>
<td>13 (31.7)</td>
</tr>
<tr>
<td>Stiff fingers or arms</td>
<td>12 (29.3)</td>
</tr>
<tr>
<td>Dizzy spells</td>
<td>12 (29.3)</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>10 (24.4)</td>
</tr>
<tr>
<td>Chest pain</td>
<td>9 (22.0)</td>
</tr>
<tr>
<td>Feeling confused</td>
<td>6 (14.6)</td>
</tr>
<tr>
<td>Tight feelings around mouth</td>
<td>4 (9.8)</td>
</tr>
<tr>
<td>Other items</td>
<td></td>
</tr>
<tr>
<td>Sighing</td>
<td>19 (48.7)</td>
</tr>
<tr>
<td>Yawning</td>
<td>18 (46.2)</td>
</tr>
</tbody>
</table>
Our patients had a systematic measurement of output due to deconditioning or abnormal muscle O2 uptake. Our patients had a systematic measurement of output due to deconditioning or abnormal muscle O2 uptake. This pattern suggests an abnormal cardiac pathologies, abnormal arterial desaturation (22.9%). After exclusion of main causes, including utilisation/delivery limitation was present in 11 patients respectively. Whether specific damage to respiratory centres is present in patients with DB remains unknown and needs to be investigated. Another possible explanation for hyperventilation could be local muscular mechanisms with increased sensitive afferents signals to the respiratory centre leading to higher ventilation.34

Interestingly, PFTs (including a systematic measurement of TLCO) without interstitial abnormalities or in those with low transfer coefficient of the lung for carbon monoxide (KCO) without interstitial abnormalities or in those with a history of pulmonary embolism during SARS-CoV-2 with a diagnostic algorithm suggested elsewhere.37 Seven patients (14.6%) with concomitant controlled asthma were included. None had obstructive spirometry and all patients described their symptoms as different from those of asthma.

Online supplemental material 1 describes in detail our diagnostic process, including objective definitions (when applicable) of the different CPET patterns, as well as a description of some patients in our case series. Although inspiratory capacity measurements are recommended in respiratory diseases,25 we considered that it could modify our interpretation of DB (including sighs and subjective analysis of the VT variability) and it was not performed.

The strengths of the study are the size of the case series, the systematic assessment of symptoms, QoL and functional repercussions, and the complete approach to diagnose DB, including a detailed analysis of CPET with supplementary slopes and continuous flow-volume and volume-over-time graphs. Limitations are: (1) the absence of CPET and PFT before acute COVID-19 to evaluate for pre-existing abnormal breathing patterns and to assess PFT and exercise capacity change, (2) the monocentric evaluation that may limit the generalisability of our findings, (3) the lack of consensus objective criteria to diagnose DB, (4) the absence of a control group of healthy individuals or of post-COVID patients with respiratory symptoms but without DB and (5) the lack of a measurement that depicted the time from onset of long COVID symptoms to first assessment in the study. Therefore, we cannot assure that the full extent of was diagnosed. Our study design did not allow to differentiate between central (cardiac output) or peripheral oxygen extraction as the cause of the observed limitation. While the presence of concomitant deconditioning could explain the level of dyspnoea to some extent, it cannot explain the other associated respiratory and extrapulmonary symptoms reported by all included patients.

RL patterns during CPET were present in two patients due to a breathing reserve <15%. Both had mild COVID-19 infection with normal PFTs and imaging. They were diagnosed with an important HVS with a severe elevation of VE/VCO2 slope and respiratory alkalosis at the end of exercise, despite a normal VD/VT ratio, causing the exhaustion of breathing reserve. Five patients had an abnormal TLCO, one patient had a restriction, four patients had mild residual interstitial abnormalities and one patient had a segmental pulmonary embolism. At exercise, none of these patients had gas exchange abnormalities or obvious ventilatory constraints, including VT plateau or exhaustion of breathing reserve. Symptoms, VD/VT and other criteria of ventilatory inefficiency were carefully investigated before hyperventilation was diagnosed.12 36 We also excluded SARS-CoV-2-induced vascular sequelae in patients with low TLCO due to a low transfer coefficient of the lung for carbon monoxide (KCO) without interstitial abnormalities or in those with a history of pulmonary embolism during SARS-CoV-2 with a diagnostic algorithm suggested elsewhere.37 Seven patients (14.6%) with concomitant controlled asthma were included. None had obstructive spirometry and all patients described their symptoms as different from those of asthma.

Table 4 Mental and physical wellness scores at first consultation

<table>
<thead>
<tr>
<th></th>
<th>Dysfunctional breathing (N=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HADS score, median (IQR)</strong></td>
<td></td>
</tr>
<tr>
<td>HADS, anxiety</td>
<td>9 (6.2)</td>
</tr>
<tr>
<td>HADS, depression</td>
<td>7.5 (5.2)</td>
</tr>
<tr>
<td>Total score</td>
<td>16.5 (11)</td>
</tr>
<tr>
<td><strong>Anxiety and/or depression risk, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Low (&lt;11)</td>
<td>11 (22.9)</td>
</tr>
<tr>
<td>Moderate (11-14)</td>
<td>7 (14.6)</td>
</tr>
<tr>
<td>Severe (≥15)</td>
<td>30 (62.5)</td>
</tr>
<tr>
<td><strong>SF-36 score by domains, median (IQR)</strong></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>55 (37.5)</td>
</tr>
<tr>
<td>Role limitation (physical)</td>
<td>0 (25)</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>41 (34.5)</td>
</tr>
<tr>
<td>General health</td>
<td>50 (26)</td>
</tr>
<tr>
<td>Vitality</td>
<td>20 (20)</td>
</tr>
<tr>
<td>Social functioning</td>
<td>37.5 (25)</td>
</tr>
<tr>
<td>Role limitation (emotional)</td>
<td>33.3 (66.8)</td>
</tr>
<tr>
<td>Mental health</td>
<td>52 (16)</td>
</tr>
<tr>
<td><strong>PCFS scale, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>1</td>
<td>12 (25.5)</td>
</tr>
<tr>
<td>2</td>
<td>15 (31.9)</td>
</tr>
<tr>
<td>3</td>
<td>19 (40.4)</td>
</tr>
<tr>
<td>4</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

HADS, Hospital Anxiety and Depression Scale; PCFS scale, Post-COVID-19 Functional Status Scale; SF-36, Short-Form Health Survey.


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symptoms, QoL and post-COVID functional impact were not evolving before the clinical evaluation.

While objective criteria to help the diagnosis of HVS have been described, there are no validated objective criteria for the diagnosis of EB/PDS. Hence, we probably used the most appropriate diagnostic approach, which is a combined approach of clinical symptoms and evaluation of breathing pattern at rest and during exercise after exclusion of other possible causes for the symptoms. The lack of a control group is a limitation that precludes the understanding of the exact extent of symptoms attributable to the diagnosis of DB. However, we believe that this case series is still of great value to highlight the major impact associated with the diagnosis of DB that concerned 32.4% of our ambulatory patients presenting with unexplained dyspnoea.

CONCLUSION

One-third of patients with long COVID-associated dyspnoea presented with HVS, EB/PDS or a mix of these two patterns. Patients with DB had a high burden of respiratory and general symptoms, with a high functional impact and a low QoL. Recognition of DB associated with long COVID is important for the design of therapeutic trials and to foster research on the potential mechanisms of its occurrence.

Figure 2 Mean SF-36 values by domain, sex and dysfunctional breathing status. BP, bodily pain; GH, general health; MH, mental health; PF, physical functioning; RE, role limitations (emotional); RP, role limitations (physical); SF, social functioning; SF-36, 36 Short Form Health Survey; VT, vitality. Controls’ data were taken from a 2007 study on 2093 healthy never-smoker adults in Switzerland.29

Author affiliations
1Service de pneumologie, Hôpital de Sion Centre Hospitalier du Valais Romand, Sion, Switzerland
2Service de pneumologie, département des spécialités de médecine interne, Hôpitaux universitaires de Genève, Genève, Switzerland
3University of Geneva, Faculty of Medicine, Geneva, Switzerland
4Service de pneumologie, Hôpital Riviera-Chablais, Rennaz, Switzerland
5Service de Physiothérapie, Hôpital de Sion, Centre Hospitalier du valais Romand, Sion, Switzerland

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Contributors LG, IF and P-OB designed the study and drafted the manuscript. MA handled the database and ran the statistical analysis. MA, SL, AB, SV and GG revised the work, contributed to critical appraisal and enriched the literature search. All authors reviewed and revised the manuscript and approved the final version. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. P-OB accepts full responsibility for the work and the conduct of the study, had access to the data and controlled the decision to publish.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by (Commission cantonale d’éthique de la recherche sur l’être humain (CER VD), ID: 2021-01688). Participants gave informed consent to participate in the study before taking part.
### Table 5  Pulmonary function tests and cardiopulmonary exercise test parameters

<table>
<thead>
<tr>
<th>Periodic deep sighing (N=22)</th>
<th>Hyperventilation (N=10)</th>
<th>Mixed (N=16)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pulmonary function tests</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FVC, % predicted value, median (IQR)</td>
<td>102 (10.7)</td>
<td>99 (16)</td>
<td>103 (14.7)</td>
</tr>
<tr>
<td>FEV1, % predicted value, median (IQR)</td>
<td>104 (17)</td>
<td>95.5 (16.7)</td>
<td>100 (16.5)</td>
</tr>
<tr>
<td>FEV1/FVC, Z score &lt;1.64, yes, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>FEV1/FVC, %, median (IQR)</td>
<td>83.4 (7.8)</td>
<td>82.3 (3.3)</td>
<td>79.5 (7.7)</td>
</tr>
<tr>
<td>TLC, Z score&lt;1.64, yes, n (%)</td>
<td>0 (0)</td>
<td>1 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>TLC, % predicted value, median (IQR)</td>
<td>101 (11)</td>
<td>99.5 (7)</td>
<td>107 (16)</td>
</tr>
<tr>
<td>TLCO, Z score&lt;1.64, yes, n (%)</td>
<td>1 (4.5)</td>
<td>2 (22.2)</td>
<td>2 (13.33)</td>
</tr>
<tr>
<td>TLCO, % predicted value, median (IQR)</td>
<td>94 (14.7)</td>
<td>87 (12)</td>
<td>88 (13.5)</td>
</tr>
<tr>
<td><strong>Cardiopulmonary exercise testing</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximal effort, n (%)*</td>
<td>21 (95.4)</td>
<td>8 (80)</td>
<td>13 (81.2)</td>
</tr>
<tr>
<td>Exercise capacity, median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak V'O₂, mL/min/kg</td>
<td>23.8 (8.9)</td>
<td>21.7 (3.9)</td>
<td>21 (13)</td>
</tr>
<tr>
<td>Peak V'O₂, % predicted value*</td>
<td>94.8 (28.2)</td>
<td>79.3 (16.9)</td>
<td>85.1 (19.7)</td>
</tr>
<tr>
<td>Peak charge, watt</td>
<td>150 (50.5)</td>
<td>128.5 (42)</td>
<td>138 (36.7)</td>
</tr>
<tr>
<td>Peak charge, % predicted value*</td>
<td>103.5 (29)</td>
<td>87 (15)</td>
<td>82 (35)</td>
</tr>
<tr>
<td>Cardiovascular, median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak HR, bpm</td>
<td>154.5 (20)</td>
<td>155 (14.5)</td>
<td>151 (38.7)</td>
</tr>
<tr>
<td>Peak O₂ pulse, ml/pulse</td>
<td>12.3 (4.9)</td>
<td>9.2 (2.8)</td>
<td>11.1 (5.5)</td>
</tr>
<tr>
<td>Ventilation, median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak VE, L/min</td>
<td>78.5 (28.2)</td>
<td>69.5 (28.5)</td>
<td>75.5 (20.5)</td>
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<tr>
<td>Peak VT, L</td>
<td>2.08 (0.8)</td>
<td>1.71 (0.7)</td>
<td>2.04 (0.7)</td>
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<tr>
<td>Peak BF, /min</td>
<td>37.50 (9.2)</td>
<td>41 (9.5)</td>
<td>37 (9)</td>
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<tr>
<td>Peak RER</td>
<td>1.17 (0.12)</td>
<td>1.11 (0.08)</td>
<td>1.11 (0.16)</td>
</tr>
<tr>
<td>V'E/V'CO2 slope</td>
<td>24.9 (3.9)</td>
<td>38.9 (9.3)</td>
<td>36.4 (10.1)</td>
</tr>
<tr>
<td>V'E/V'CO2 intercept</td>
<td>5.4 (4.5)</td>
<td>3.1 (3.8)</td>
<td>2.7 (2.2)</td>
</tr>
<tr>
<td>Peak breathing reserve, (%)</td>
<td>32 (15.2)</td>
<td>31.5 (25.5)</td>
<td>36.5 (15.5)</td>
</tr>
<tr>
<td>Arterial blood gases, median (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resting pH</td>
<td>7.43 (0.04)</td>
<td>7.46 (0.06)</td>
<td>7.43 (0.02)</td>
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<tr>
<td>Resting PaO₂, kPa</td>
<td>12.3 (1.91)</td>
<td>12.2 (0.28)</td>
<td>12.1 (2.2)</td>
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<tr>
<td>Resting PaCO₂, kPa</td>
<td>4.88 (0.8)</td>
<td>4.57 (0.84)</td>
<td>4.72 (0.55)</td>
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<tr>
<td>Peak pH</td>
<td>7.3 (0.05)</td>
<td>7.37 (0.05)</td>
<td>7.34 (0.03)</td>
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<tr>
<td>Peak PaO₂, kPa</td>
<td>13.3 (1.1)</td>
<td>13.35 (1.93)</td>
<td>14.1 (2.15)</td>
</tr>
<tr>
<td>Peak PaCO₂, kPa</td>
<td>4.27 (1.19)</td>
<td>3.67 (0.58)</td>
<td>4.1 (0.92)</td>
</tr>
<tr>
<td>Peak lactates, mmol/L</td>
<td>10.7 (3.12)</td>
<td>8.6 (3.09)</td>
<td>8.2 (5.4)</td>
</tr>
<tr>
<td>Other abnormal patterns, yes, n (%)</td>
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<td></td>
</tr>
<tr>
<td>Metabolic pattern</td>
<td>0 (0)</td>
<td>1 (10)</td>
<td>2 (12.5)</td>
</tr>
<tr>
<td>O₂ delivery/utilisation impairment‡</td>
<td>4 (18.2)</td>
<td>3 (30)</td>
<td>4 (28.6)</td>
</tr>
<tr>
<td>Chronotrophic incompetence§</td>
<td>1 (4.5)</td>
<td>0 (0)</td>
<td>1 (7.1)</td>
</tr>
<tr>
<td>Significant arrhythmia¶</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (12.5)</td>
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<tr>
<td>Signs of ischaemic heart disease</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
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</table>

Continued
Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

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Table 5 Continued

<table>
<thead>
<tr>
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<th>Hyperventilation (N=10)</th>
<th>Mixed (N=16)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>P values were computed by Kruskal-Wallis rank sum test for numerical data and by Fisher’s exact test for categorical data. *According to the ERS statement on the standardisation of cardipulmonary exercise testing in chronic lung diseases. †Defined as the presence in an obese patient (BMI≥30kg/m²) of a high cost of unloading pedalling and a dissociation between predicted maximal load and predicted peak V̇O₂. ‡Defined as a low V̇O₂ (≤84% of predicted) due to a low V̇O₂ pulse in an objectively maximal test or a low anaerobic threshold ≤50%. §Defined as a low heart rate (≤80% of predicted) in an objectively maximal test. ¶In both cases, frequent premature ventricular contractions. BF, breathing frequency; BMI, body mass index; ERS, European Respiratory Society; FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; RER, respiratory exchange ratio; TLC, total lung capacity; TLCO, diffusing capacity of lung for carbon monoxide; VE, minute ventilation; VT, volume tidal.</td>
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</tbody>
</table>

REFERENCES

Table 6 Other investigations

<table>
<thead>
<tr>
<th>Dysfunctional breathing (N=48)</th>
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<tbody>
<tr>
<td>Blood results</td>
</tr>
<tr>
<td>Hb, g/L, median (IQR)</td>
</tr>
<tr>
<td>Anaemia, n (%)*</td>
</tr>
<tr>
<td>NT-proBNP, ng/L, median (IQR)</td>
</tr>
<tr>
<td>NT-proBNP&gt;125ng/L, n (%)</td>
</tr>
<tr>
<td>Echocardiography</td>
</tr>
<tr>
<td>Radiology</td>
</tr>
<tr>
<td>Chest X-ray, n (%)</td>
</tr>
<tr>
<td>Normal</td>
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<tr>
<td>Abnormal</td>
</tr>
<tr>
<td>Chest scan, n (%)†</td>
</tr>
<tr>
<td>No examination</td>
</tr>
<tr>
<td>Abnormal‡</td>
</tr>
</tbody>
</table>

*Anaemia defined as haemoglobin level strictly inferior to 12 g/L in women and 13 g/L in men. †Five tests with contrast product. ‡One patient with segmental pulmonary embolism, four patients with parenchymal abnormalities. Hb, haemoglobin; NT-ProBNP, N-terminal prohormone of brain natriuretic peptide.

ORCID iDs
Léon Genecand http://orcid.org/0000-0001-6965-0480
Pierre-Olivier Brildevaux http://orcid.org/0000-0002-8021-0950