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Movement Disorders
CLINICAL PRACTICE

RESEARCH ARTICLE

Respiratory Dysfunction and Abnormal Hypoxic Ventilatory Response in Mild to Moderate Parkinson's Disease

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Abstract: Background: Respiratory dysfunction is an important contributor to morbidity and mortality in advanced Parkinson's disease (PD), but it is unclear what parameters are sensitive to diagnose and monitor respiratory dysfunction across disease phases.

Objectives: We aimed to characterize respiratory dysfunction in mild to moderate PD.

Methods: In 20 individuals without cardiopulmonary comorbidity, pulmonary and inspiratory muscle function testing were performed ON-medication. Subsequently, the acute ventilatory response to hypoxia (HVR) was assessed by gradually decreasing F_IO_2 from 0.209 (room air) to 0.127, which was compared to eight age- and sex-matched healthy controls under arterial blood gas monitoring. Lastly, on different days, the same 20 individuals with PD underwent six blinded exposures to 45-min normobaric hypoxia at FiO2 0.163 and 0.127 or placebo OFF-medication to assess breathing responses.

Results: At rest, individuals with greatest PD severity had a lower tidal volume (pairwise comparisons: 0.59 vs. 0.74, $P = 0.038$–0.050) and tended to have a higher breathing frequency (17.7 vs. 14.4, $P = 0.076$), despite normal pulmonary function. A 45-min exposure to hypoxia induced a significantly lower acute HVR in individuals with PD compared to controls (−0.0489 vs. 0.133 L.min/%, $P = 0.0038$). Acute HVR was reduced regardless of disease severity. Subacute HVR in individuals with milder disease tended to be higher compared to those with more advanced disease ($P = 0.079$).

Conclusions: Respiratory dysfunction is present in individuals with PD, including those with relatively mild disease severity, and is characterized by altered breathing patterns at rest, as well as a lower HVR, despite normal pulmonary and inspiratory muscle function testing.

Respiratory dysfunction is highly prevalent among individuals with Parkinson's disease (PD) in advanced disease stages.[1,2] Respiratory involvement can become apparent through abnormal pulmonary function tests or respiratory symptoms and, combined with dysphagia, constitutes an important predictor of aspiration pneumonia in PD. Consequently, risk of aspiration pneumonia in PD is four times higher compared to matched controls, and aspiration pneumonia accounts for the majority of deaths in PD.[3,4]

Studies examining respiratory function in early PD have primarily been conducted using spirometry, which demonstrate a gradual annual decline in maximum voluntary ventilation,

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decreased maximum inspiratory pressure and inspiratory muscle weakness unrelated to lower static long volumes.[5–8] The observed impairments in PD have typically been attributed to peripherally impaired respiratory mechanics due to chest-wall rigidity.[1,9] Although spirometry is a valid standardized diagnostic and monitoring tool, spirometry does not give insight into (resting) breathing patterns and primarily tests peripheral aspects of respiratory function. As a result, relatively little is known about the impact of PD on both peripheral factors (eg, muscle weakness, chest wall rigidity) and the centrally regulated neural control of breathing, which is relevant as these factors may contribute to respiratory dysfunction in PD.[2] The increased respiratory drive and changes in breathing patterns observed in advanced PD might be a reflection of a dysfunctional central regulation of breathing, which constitutes a reflex arc from carotid body chemoreceptors to medullary respiratory motor efferents.[7,10] This pathway is activated by changes in oxygen availability or demand, and its function can therefore be investigated by measuring the hypoxic ventilatory response (HVR). To date, only few small-sized studies investigated HVR in PD and showed conflicting results.[11–13]

In this study, we aimed to characterize respiratory dysfunction in 20 individuals with mild to moderate PD without cardiopulmonary comorbidity by conducting pulmonary function testing, measuring breathing patterns at rest and comparing ventilatory responses to normobaric hypoxia to age- and sex-matched controls. We hypothesize disease severity-dependent aberrant breathing patterns at rest as well as a reduced HVR in persons with PD compared to controls.

Methods

This study is part of a clinical trial, which has been reviewed and approved by the Medical Research Ethics Committee East Netherlands, The Netherlands, (reference number NL.77891.091.22) and has been registered at clinicaltrials.gov (NCT05214287, registered January 28, 2022). The protocol and statistical analysis plan are available open access.[14] Participants received verbal and written information about the study and written informed consent was obtained before screening.

Study Population

Individuals with clinically established PD and Hoehn and Yahr (H&Y) scores between 1.5 and 3 were included. H&Y 3 reflects the highest disease severity, indicating that an individual has bilateral symptoms and balance problems, and H&Y 1.5 indicates a still unilateral disease and some axial symptoms, such as gait disturbance. These all included individuals of a randomized controlled trial of hypoxic conditioning in PD.[14] Hypoxic conditioning involves the controlled exposure to moderate hypoxia in repeated bouts. Exclusion criteria are comprehensively discussed elsewhere.[14] Briefly, individuals were excluded when they had comorbid respiratory disease (eg, asthma, COPD), current or recent cigarette use, cardiac rhythm abnormalities and congestive heart failure and unstable dopaminergic medication. Lastly, individuals with subjective questionnaire-based respiratory symptoms in the OFF state were excluded to decrease burden of trial participation.

Eight age- and sex-matched healthy individuals were included during the study as a control group only to compare hypoxic ventilatory response with PD participants. Control group size was based on a power calculation to detect differences in hypoxic ventilatory response between people with PD and the matched control group, assuming an HVR slope ≥ 0 in the control group (vs. the negative slope in the PD group), an alpha of 0.05 and identical standard error to the PD group of 0.0040.

Study Procedures

Pulmonary Function Testing

Participants with PD underwent pulmonary function tests using spirometry to measure FEV1, TLC, maximum inspiratory pressure (MIP) and peak cough flow (L/min) in the ON condition. Additionally, a carbon monoxide diffusion test was performed. Subsequent hypoxic interventions (see below) were only conducted when spirometry and diffusion tests were within predefined levels that can be classified as normal for safety purposes, and to exclude abnormal spirometry or diffusion as causes of the hypothesized decreased HVR or breathing pattern changes. ATS/ERS guidelines were followed while conducting and interpreting these tests.[15]

Breathing at Rest and during Continuous Hypoxia

We investigated breathing patterns and signs of hypoxemia at rest and during hypoxic exposure in participants with PD OFF-medication. These participants were blinded to 45-min continuous hypoxic exposures at F_IO_2 0.127 and 0.163, and to F_IO_2 0.209 (room air) in a randomized sequence. All participants underwent every protocol twice (totaling six interventions per participant). Signs of hypoxemia at rest (in room air) were measured by arterial blood gas, peripheral oxygen saturation (SpO2) and serum erythropoietin (EPO) as an extra marker of activation of the hypoxia response cascade.

Experimental days were separated at least 5 days from each other as a wash-out, to avoid lingering effects of the intervention on respiratory parameters. Participants with PD were in a practically defined OFF state during these interventions (>12 h after last dopaminergic medication). Success of blinding was assessed by asking participants to guess the correct intervention sequence. Blinding was effective, as the number of interventions guessed correctly was lower than chance (19.5%).

Hypoxic Ventilatory Response Compared to Matched Controls

Keeping with the proposed structure with testing days being separated at least 5 days from any other hypoxia intervention, individuals with PD and healthy controls were blindly exposed to a

1-h test of hypoxic ventilatory response by administering gradually decreasing levels of F_IO_2 at 0.163, 0.150, 0.138 and 0.127, or until an arterial oxygen saturation (SaO_2) <80% or an oxygen pressure (pO_2) <5.3 kPa was reached. In both groups, participants remained at each F_IO_2 level for at least 10 min to allow for acclimatization before proceeding to the next level. At every F_IO_2 level, an arterial blood gas was taken. During this test, participants were allowed to use their regular dopaminergic medication to ensure that the results of the study are translatable to a real-world situation for patients with PD.

Equipment

Hypoxic interventions were performed on an ISO 13485:2016 certified hypoxic generator (b-Cat ALT-120, B-cat High Altitude, Tiel, the Netherlands) that uses pressure swing adsorption to reduce the F_IO_2 of room air at normobaric pressures (Nijmegen, 20 meters above sea level). The generator was connected to two 50 L reservoir bags and a mouth and nose mask (Hans Rudolph 7450 Series V2 Oxygen Mask®). F_IO_2, SpO_2, minute ventilation, breathing frequency, tidal volume and heart rate were measured breath-by-breath using the Quark cardiopulmonary exercise testing (CPET) metabolic cart for cardiopulmonary testing, (COSMED Srl, The Metabolic Company, Italy). Stop criteria are detailed elsewhere.[14]

Data and Sample Collection

Continuous data from CPET were extracted and every 5 min, 2-minute intervals of respiratory parameter measurements were selected independently by two researchers (JJD and IS). For the intervention with gradually decreasing F_IO_2 levels, selections were taken near the end of every F_IO_2 level interval just before switching to a lower F_IO_2 level to exclude the cardiopulmonary adaptation phase to any new F_IO_2 level. Arterial pH, pCO_2, pO_2, HCO_3- and SaO_2 were measured using the point-of-care i-STAT 1 blood analyzer (Abbott Laboratories, Illinois, USA) using CG4+ cartridges at every F_IO_2 level.

Blood samples were refrigerated for 30–90 min, then centrifuged for 10 min at 2000 *g* at 4°C and stored at −80°C until batch analysis. EPO concentrations were analyzed using the Human EPO ELISA kit from *ThermoFisher* according to manufacturer's instructions. For every participant, the two EPO measurements were averaged before group-level analysis.

Statistical Analysis

Between-group baseline characteristics and breathing-at-rest parameters for PD participants were analyzed using ANOVA, followed by post-hoc tests to evaluate pairwise comparisons in the case of a significant ANOVA. HVR was modeled for every individual using linear regression, where the slope of the ventilation-SpO_2 graph was considered the HVR. HVR of individuals with PD and controls were compared using independent *t*-tests, whereas HVR and blood gas parameters of individuals with different PD severity were compared using ANOVA. $P < 0.05$ was considered statistically significant. Analyses were conducted using R. GraphPad Prism 9 was used for graph visualization.

Results

Pulmonary Function Testing

Baseline characteristics, pulmonary function testing results and parameters for breathing at rest were tested in 20 participants

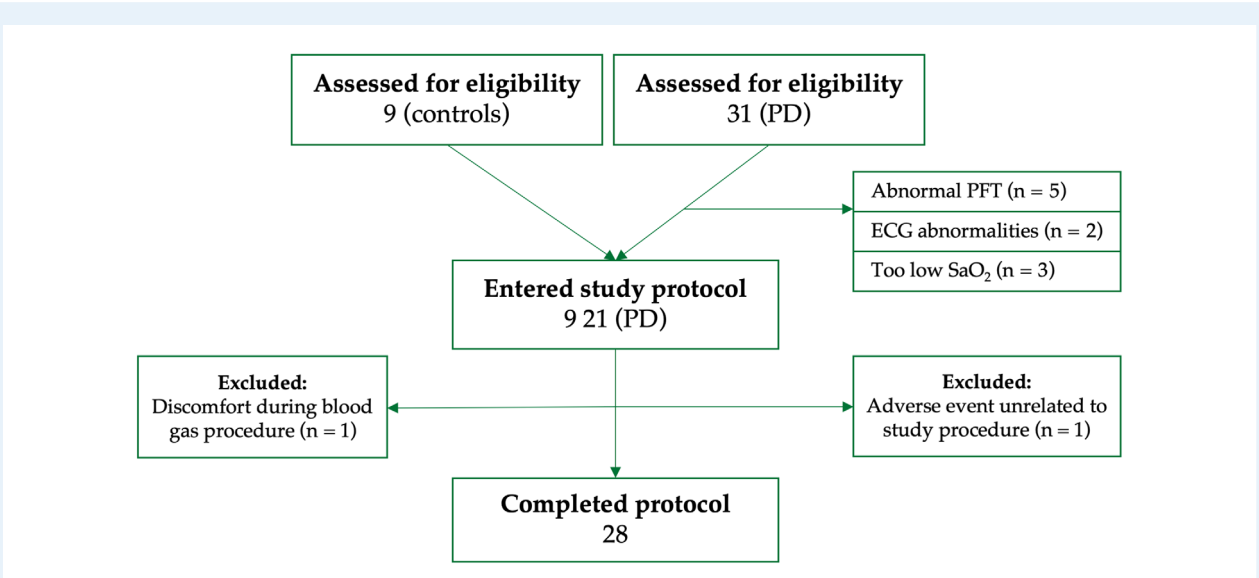

Figure 1. Flowchart of participant selection.

with PD and are detailed in Fig. 1 and Table 1. Participants with the greatest disease severity (H&Y 3) were significantly shorter compared to the other groups (pairwise comparisons: $P = 0.01$–0.04). Although vital capacity ($P = 0.030$ for H&Y 1.5–2 vs. 3) and diffusion capacity ($P = 0.018$ between H&Y 1.5–2 and 3) were also lower in individuals with H&Y 3, predicted values corrected for age,

TABLE 1 *Baseline characteristics, pulmonary function testing and breathing patterns at rest*

	H&Y 1.5–2 (n = 8)	H&Y 2.5 (n = 5)	H&Y 3 (n = 7)	*P*-value
Baseline characteristics				
Age, yrs	59.8 ± 6.3	64.4 ± 3.4	62.9 ± 6.7	0.364
Female, no. (%)	3 (38%)	1 (20%)	6 (86%)	
Height, cm	179.4 ± 10.8	178.9 ± 6.1	165.4 ± 6.6	**0.011**
Weight, kg	77.2 ± 12.9	82.5 ± 12.7	68.1 ± 6.8	0.098
Levodopa-equivalent daily dose (LEDD), mg	490.0 ± 431.4	225.0 ± 248.7	568.2 ± 562.5	0.78
MDS-UPDRS part III (median, IQR)[a]	41 [27.8–54.3]	45 [35.3–54.8]	49 [34.3–63.8]	**<0.005**
Pulmonary function testing				
FEV_1, L	3.61 ± 1.00	3.48 ± 0.71	2.62 ± 0.46	0.060
FEV_1, % predicted	103.88 ± 18.23	103.60 ± 10.64	102.29 ± 7.69	0.97
VC, L	4.87 ± 1.38	4.67 ± 1.07	3.29 ± 0.58	**0.028**
VC, % predicted	107.75 ± 17.56	105.80 ± 12.80	100.14 ± 9.92	0.58
FEV_1/VC, %	74.32 ± 3.91	75.17 ± 5.34	79.98 ± 4.01	0.052
FEV_1/VC, % predicted	95.63 ± 4.50	98.00 ± 6.00	101.57 ± 4.96	0.10
Peak cough flow, L/s	8.26 ± 2.28	7.97 ± 1.47	6.30 ± 1.01	0.10
DLCO, mmol/(min × kPa)	9.27 ± 2.32	8.05 ± 0.60	6.79 ± 0.63	**0.023**
DLCO, % predicted	103.13 ± 12.80	92.60 ± 14.35	98.57 ± 11.97	0.38
KCO, mmol/((min × kPa × L)	1.39 ± 0.24	1.29 ± 0.24	1.45 ± 0.17	0.50
KCO, % predicted	99.50 ± 14.64	94.40 ± 17.50	103.00 ± 10.46	0.59
MIP, %[a]	8.29 ± 2.82	6.86 ± 1.90	5.87 ± 2.16	0.20
MIP, % predicted[b]	95.88 ± 37.55	75.20 ± 16.47	80.17 ± 30.75	0.47
Breathing at rest				
Ventilation, L/min	10.24 ± 2.08	10.34 ± 1.03	10.02 ± 1.79	0.95
Breathing frequency, /min	14.36 ± 2.48	14.38 ± 3.35	17.71 ± 3.03	0.076
Tidal volume, L/breath	0.74 ± 0.11	0.77 ± 0.15	0.59 ± 0.09	**0.023**★
SpO_2, %	97.25 ± 0.94	97.54 ± 0.76	96.51 ± 0.89	0.13
Arterial blood gas at rest				
SaO_2, %	96.6 ± 1.2	97.0 ± 0.0	96.29 ± 0.76	0.40
pO_2, kPa	11.59 ± 2.23	11.94 ± 0.34	11.61 ± 0.87	0.91
pCO_2, kPa	5.83 ± 1.35	5.63 ± 0.44	5.33 ± 0.46	0.52
HCO_3-, kPa	25.0 ± 1.14	26.96 ± 1.86	25.20 ± 2.34	0.14
pH	7.39 ± 0.02	7.41 ± 0.01	7.41 ± 0.03	0.23
Serum EPO, mIU/mL	8.84 ± 3.51	9.11 ± 2.93	10.04 ± 4.95	0.84

Abbreviations: EPO, erythropoietin; MDS-UPDRS, movement disorders society, unified Parkinson's disease rating scale.
[a]Not normally distributed.
[b]Missing data from one participant.
★Pairwise comparisons $P = 0.050$ (H&Y 1.5–2 vs. 3) $P = 0.038$ (H&Y 2,5 vs. 3) $P = 0.90$ (H&Y 1.5–2 vs. 2.5) bold = $P < 0.05$.

weight and height did not differ significantly between groups. There were no signs of respiratory obstruction with increasing disease severity, although peak cough flow tended to be lower with higher disease severity ($P = 0.10$).

Breathing Patterns at Rest

Resting breathing patterns differed between participants with PD (Table 1). Tidal volume was lower ($P = 0.023$, pairwise comparisons $P = 0.038$–0.050) and breathing frequency tended to be higher ($P = 0.076$) when compared between H&Y 3 and lower disease severity groups. Ventilation, the product of tidal volume and breathing frequency, did not differ between PD subgroups ($P = 0.95$). SpO_2 ($P = 0.13$) and EPO ($P = 0.84$), as indicator of hypoxia at rest, did not differ between disease severity groups.

Acute Hypoxic Ventilatory Response

Eight healthy controls were matched for age and sex and underwent HVR testing (Table 2). Accurate data for HVR analysis were available for all matched controls, but two participants with PD were excluded from this analysis because of unreliable tidal volume measurements from the metabolic cart.

Acute HVR was analyzed by gradually decreasing F_IO_2 from room air (0.209) to 0.127 during a 1-h hypoxic test in ON-medication conditions. HVR was significantly lower in PD compared to healthy controls ($P = 0.0038$, Fig. 2), also when excluding eight individuals with PD that did not reach the lowest F_IO_2 of 0.127 ($P = 0.0062$) because SpO_2 or pO_2 reached stop criteria. Specifically, ventilation in people with PD paradoxically decreased upon exposure to gradually decreasing F_IO_2 (−0.0489 L/min per SpO_2 percentage point decrease, or L.min/%, $P = 0.0011$ for difference from zero, Fig. 2). In contrast, controls demonstrated a non-significant increase in ventilation upon reduction of F_IO_2 (133 mL increase per SpO_2 percentage point, $P = 0.053$). Individuals with PD had lower SpO_2 at F_IO_2 0.127 compared to controls ($P = 0.036$). We found no significant differences in HVR between PD severity groups ($P = 0.18$ and $P = 0.54$ for SpO_2 and SaO_2, Fig. S1) or between individuals that already had a SpO_2 or SaO_2 near 80% (stop criterion) before F_IO_2 0.127 was reached ($P = 0.85$, Fig. S2). With regard to blood gas parameters, ventilatory response as a function of SaO_2 was not statistically significant ($P = 0.19$, Fig. S3). $PaCO_2$ did not significantly change in PD or controls and was not significantly different between groups ($P = 0.11$, Fig. S4). Similarly, HCO_3^- did not significantly change during the intervention and did not differ between PD and controls ($P = 0.84$), whereas pH tended to slightly increase in PD compared to controls (0.003 vs. 0.002 L/min per point decrease in F_IO_2, $P = 0.025$).

Ventilatory Response to Continuous Hypoxia

Ventilatory response to continuous hypoxia (at stable F_IO_2) in PD participants OFF-medication was investigated by blindly administering 45-min protocols at room air, F_IO_2 0.163 and F_IO_2 0.127 twice, with tests being at least 5 days apart. Tidal volume, breathing frequency, and ventilation of these interventions (n = 120) remained constant at the group level during the 45-min exposure, apart from a transient non-significant higher ventilation at F_IO_2 0.127 that is fully explained by a higher tidal

TABLE 2 *Individuals with PD versus controls*

	PD (n = 20)	Controls (n = 8)	*P*-value
Age	62 ± 5.9	63.6 ± 6.8	0.53
Female, no. (%)	9 (45%)	4 (50%)	
Height	174.4 ± 10.5	176.6 ± 8.3	0.60
Weight	75.3 ± 12.0	70.6 ± 6.7	0.31
Breathing at rest			
Ventilation, L/min	10.83 ± 3.04	8.98 ± 1.82	0.12
Breathing frequency, /min	17.2 ± 4.0	14.2 ± 1.7	0.052
Tidal volume, mL	0.66 ± 0.17	0.65 ± 0.16	0.82
SpO_2, %	96.61 ± 1.40	96.73 ± 1.17	0.83
Arterial blood gas at rest			
SaO_2, %	96.6 ± 0.88	96.88 ± 1.13	0.50
pO_2, kPa	11.68 ± 1.63	12.06 ± 1.27	0.56
PCO_2, kPa	5.64 ± 1.02	5.29 ± 0.55	0.37
HCO_3^-, kPa	25.49 ± 2.02	25.14 ± 2.46	0.70
pH	7.40 ± 0.02	7.40 ± 0.02	0.59

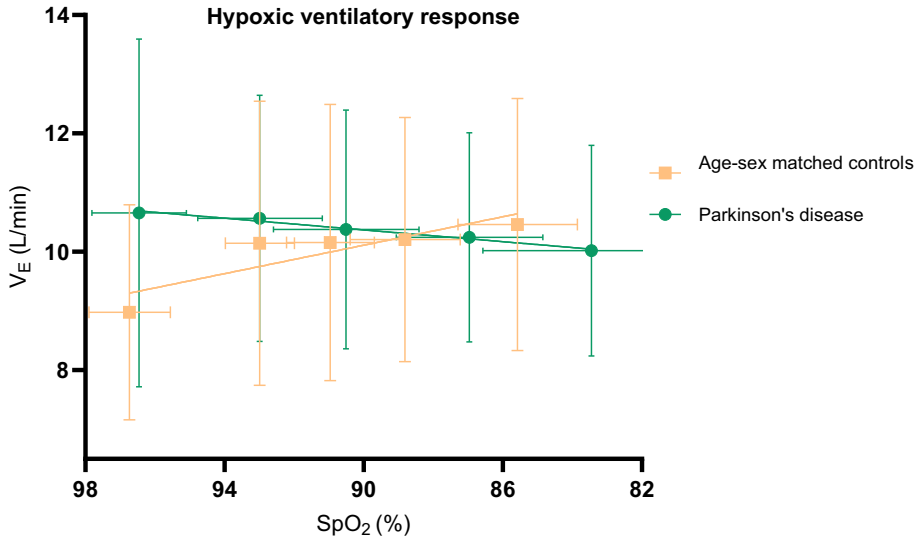

Figure 2. Difference in hypoxic ventilatory response ($P = 0.0038$) between participants with PD (N = 18) and controls (n = 8), as illustrated by the relation between peripheral oxygen saturation (SpO_2) and ventilation (V_E) at F_IO_2 levels of 0.209 (room air), 0.163, 0.15, 0.138 and 0.127 (or 0.133 when SpO_2 reaches 80% before F_IO_2 0.127). Horizontal error bars reflect the distribution of SpO_2 values at every F_IO_2 level.

volume (Fig. S5). During the longer-term 45-min exposure to F_IO_2 0.127, ventilation response tended to differ between groups ($P = 0.079$, Fig. S6).

Discussion

In this study, we characterized respiratory dysfunction in mild to moderate PD and made the following observations. First, we found that traditional measures of pulmonary function did not differ between individuals with PD and healthy controls. Second, we demonstrated distinct breathing patterns at rest in PD patients with H&Y 3, which are characterized by high breathing frequency and low tidal volume. Third, individuals with PD demonstrated a lower hypoxic ventilatory response than their age and sex-matched controls, despite being without cardiorespiratory comorbidity and despite having a normal pulmonary function following traditional measures. Specifically, individuals with PD even demonstrated an unexpected *decline* in ventilation upon exposure to increasing levels of hypoxia compared to controls. Taken together, these data highlight the presence of respiratory dysfunction in moderate PD, even in the absence of abnormal traditional pulmonary spirometry function deficits.

Following traditional pulmonary function testing, we observed a trend towards lower peak cough flow with greater disease severity. This represents a potentially relevant finding, as cough and swallowing impairment are important risk factors for aspiration pneumonia in PD.[16] However, other parameters of pulmonary function tests were normal, suggesting that traditional pulmonary function testing is not sensitive to respiratory dysfunction in early disease stages. We hypothesize that this higher sensitivity might be due to the more complex nature of forced coughing tasks. Although previous studies in individuals with PD showed a reduction of both maximum voluntary ventilation,[8,17] maximum inspiratory pressure[1,7] and vital capacity,[1] we could not corroborate the two latter findings in our study.

Despite normal pulmonary function tests, we observed remarkable differences in breathing patterns among people with moderate PD, which are reminiscent of previous findings in people with more advanced disease. Possibly, our observations may be indicative for an early form of rapid shallow breathing, a dysfunctional breathing pattern that is often an early sign of respiratory failure.[18] Indeed, such breathing patterns were recently described in people with advanced PD, including respiratory symptoms.[10] The causes of this breathing pattern are unclear, but previous studies have linked such patterns to inspiratory muscle fatigue[19] or an adaptive energy-conserving mechanism.[18] Our findings suggest that breathing patterns are altered well before (severe) respiratory symptoms and pulmonary function test deficits are present. Indeed, no individuals reported respiratory symptoms, whilst all individuals had very low scores on a respiratory screening questionnaire for PD [data not shown].[10] Therefore, alternatively, we hypothesize that such breathing patterns are due to impaired proprioceptive processing, as seen in PD-related gait impairment and hypophonia.[20,21] This hypothesis is supported by a qualitative study that suggests that this hypokinetic breathing with resulting low tidal volumes is caused by a loss of breathing automatism, which improves with conscious breathing.[10] Interestingly, a recent study revealed that nocturnal breathing patterns may possess predictive capacity for PD diagnosis, suggesting the potential sensitivity of respiratory disturbances as clinical PD biomarker.[22]

The lower HVR in people with PD compared to age and sex-matched controls is in line with some,[11,12] but not all studies.[13] A lower HVR alone cannot differentiate between peripheral and central causes in the response arc. However, our observations of a normal pulmonary function testing and lower HVR suggests that, in addition to peripheral rigidity, abnormalities in central regulatory breathing systems (ie, the neural control of breathing) might be altered early in the PD disease course. The impairment of central breathing systems in PD is also supported by preclinical evidence.[23,24] Furthermore, previous studies have demonstrated that repeated exposure to moderate hypoxia improves HVR in PD and spinal injury.[25–27] This is likely induced by increased sensitivity of the chemoreceptor response, either at the level of the carotid bodies or central respiratory motor output.[28] This highlights the plasticity of this central response, and therefore may provide an appealing target for respiratory rehabilitation to improve outcome of respiratory complications in individuals with PD. However, this warrants further intervention studies specifically targeted at the PD population. As subacute HVR was assessed OFF medication, we cannot exclude the possibility that increased truncal rigidity in this condition might explain part of the differences observed between disease severity groups, although the observed difference in acute HVR were conducted in ON medication conditions. Although pH tended to increase slightly in people with PD, which is not to be expected with lower ventilatory responses, $PaCO_2$ did not significantly change in people with PD or controls. All in all, such short-term hypoxia exposures lead to minor metabolic disturbances.

This study has several limitations. First, we excluded individuals with respiratory symptoms associated with (abstinence from) dopaminergic medication. Therefore, these results might not be representative of the severity of respiratory dysfunction in people with such complaints in similar disease stages, or for people with severely advanced PD. Moreover, the relation between measurements and actual onset with respiratory complications could not be assessed, although we explored the relation between our measurements and respiratory symptoms in daily life. Our measurements of pulmonary ventilation and $PaCO_2$ do not suggest that study interventions impacted alveolar ventilation, a more precise measure of ventilation as it accounts for pulmonary dead space. Furthermore, since acute HVR measurements were performed ON-medication, the lower acute HVR responses in PD may (in part) be related to their medication. Some preclinical evidence suggests that HVR may be suppressed by intravenous dopamine.[29] It should also be noted that levodopa may improve pulmonary function tests and respiratory symptoms.[30] Therefore, our results do not reflect pulmonary deficits in the OFF state, during which restrictive pulmonary deficits are likely. At the very least, our observations relate to a real-world situation, providing insight into how people with PD typically present in daily life, which is while being on their medication. As we did not measure hematocrit, we cannot control for unknown anemia that might explain the tendency towards higher EPO concentrations in individuals with higher disease severity. Nonetheless, our observations warrant further investigation into the presence of respiratory dysfunction in people with mild to moderate PD and the predictive nature of such respiratory signs for complications in later life. Although requiring special laboratory equipment, breathing patterns at rest and HVR might be convenient and sensitive tests for characterizing respiratory dysfunction in PD, warranting further study for this objective. As substantial inter-individual variability in breathing data and HVR exists, individualized measures might ultimately serve as biomarkers for personalized prevention against complications.

Author Roles

(1) Research Project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

J.M.J.D.: A, 1B, 1C, 2A, 2B, 2C, 3A
I.R.S.: 1C, 2B, 3A
H.W.H.H.: 1A, 2A, 2C, 3B
A.W.: 1C, 2B, 3A
V.W.D.: 1A, 2A, 2C, 3B
M.N.: 1A, 2A, 2C, 3B
M.J.M.: 1A, 1B, 2C, 3B
F.H.B.: 2C, 3B
M.K.: 1A, 2A, 2C, 3B
P.N.A.: 2C, 3B
B.R.B.: 1A, 1B, 2C, 3B
D.H.J.T.: 1A, 1B, 2C, 3B

Disclosures

Ethical Compliance Statement: This study was approved by the Medical Research Ethics Committee East Netherlands, The Netherlands, (reference number NL.77891.091.22) and has been registered at clinicaltrials.gov (NCT05214287, registered January 28, 2022). Participants received verbal and written information about the study and written informed consent was obtained before screening. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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Data Availability Statement

Anonymized data is shared with The Michael J. Fox Foundation for Parkinson's Research (the study funder). This data may be kept for storage at a central repository either hosted by The Michael J. Fox Foundation, its collaborators, or consultants and will be kept indefinitely. Anonymized data will be made publicly available by the Foundation for the intended use of research in Parkinson's disease as well as other biomedical research studies that may not be related to Parkinson's disease. ■

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Supporting Information

Supporting information may be found in the online version of this article.

Figure S1. Differences in hypoxic ventilatory response between disease severity groups, as illustrated by the relation between oxygen saturation [SpO_2 in panel A ($P = 0.18$), SaO_2 in panel B ($P = 0.54$)] and ventilation (V_E) at F_IO_2 levels of 0.209 (room air), 0.163, 0.15, 0.138 and 0.127, or 0.133 when SpO_2 reaches 80% before F_IO_2 0.127.

Figure S2. Stratification of study population by F_IO_2 level below which SpO_2 or SaO_2 drops below 80% during acute hypoxic ventilatory response intervention (Fig. 1 in manuscript). There is no statistically significant difference in hypoxic ventilatory response ($P = 0.85$).

Figure S3. Difference in hypoxic ventilatory response ($P = 0.18$) between participants with PD (N = 18) and controls (n = 8), as illustrated by the relation between peripheral oxygen saturation (SpO_2) and ventilation (V_E) at F_IO_2 levels of 0.209 (room air), 0.163, 0.15, 0.138 and 0.127 (or 0.133 when SaO_2 reaches 80% before F_IO_2 0.127). Horizontal error bars reflect the distribution of SaO_2 values at every F_IO_2 level.

Figure S4. $PaCO_2$ response during gradually decreasing F_IO_2 for PD (n = 18) and controls (n = 8).

Figure S5. Group-level effects of hypoxia or room air on tidal volume (A), breathing frequency (B) and ventilation (C) in people with PD (n = 20) OFF-medication.

Figure S6. Differences in ventilation in 45-minute protocols of F_IO_2 0.127 between disease severity groups ($P = 0.079$) OFF-medication.